

COMPOSITIONS AND METHODS FOR ALTERING COMPLEMENT ACTIVATION

CROSS REFERENCE TO RELATED APPLICATIONS

5 The present application claims priority to U.S. Provisional Application No. 63/601,145 filed November 20, 2023, the entire contents of which are hereby incorporated by reference in its entirety.

SEQUENCE LISTING

10 This application contains a Sequence Listing which has been submitted electronically in XML format and is hereby incorporated by reference in its entirety. The Sequence Listing XML file, created on November 20, 2024, is named 180802-055802PCT_SL.xml and is 3,905,996 bytes in size.

BACKGROUND

15 The complement system is an important part of the innate immune system and is involved in the clearance of microbes and cellular debris, as well as the activation of inflammation and diverse immune pathways. Overactivation of the complement system or inappropriate targeting to one's own cells can lead to disease; however, inhibition of
20 complement system activity has been successfully and safely shown to provide therapeutic benefit for patients suffering from an overactive complement system. Therefore, improved methods for reducing complement system activation in such patients are of interest.

SUMMARY

25 As described below, the present disclosure features compositions and methods for reducing complement activation by introducing one or more alterations into a complement factor B (CFB) polynucleotide in a cell. In particular embodiments, the invention of the disclosure features a base editor system (e.g., a fusion protein or complex comprising a programmable DNA binding protein, a nucleobase editor, and gRNA) for modifying a CFB
30 polynucleotide, where the modification is associated with reduced expression, and/or reduced activity of the factor B polypeptide encoded by the polynucleotide. Non-limiting examples of alterations include base edits.

 In one aspect, the disclosure provides a method of altering a nucleobase of a complement factor B (CFB) polynucleotide. The method involves contacting the CFB

polynucleotide with a base editor system containing one or more guide polynucleotides, or one or more polynucleotides encoding the one or more guide polynucleotides, and a base editor containing a nucleic acid programmable DNA binding protein (napDNAbp) domain and a deaminase domain, or one or more polynucleotide encoding the base editor. The method involves (a), (b), and/or (c), where in (a) the one or more guide polynucleotides targets the base editor to effect an alteration of a nucleobase of the CFB polynucleotide that:

- i. disrupts a splice site in the CFB polynucleotide, ii. alters a start codon in the CFB polynucleotide, iii. alters a TATA box in the CFB polynucleotide, and/or iv. introduces a new stop codon in the CFB polynucleotide. In (b) the deaminase domain contains a TadA variant (TadA*) containing an amino acid sequence having at least 90% sequence identity to the following TadA*7.10 amino acid sequence:

MSEVEFSHEYWMRHALTLAKRARDEREVPVGAVLVLNRRVIGEGWNRAIGLHDPTAHAEIMALRQGGLVMQNYRLIDATLYVTTFEPCVMCAGAMIHSRIGRVVFGVRNAKTGAAGSLMDVLHYPGMNHRVEITEGILADECAALLCYFFRMPRQVFNAQKKAQSSTD (SEQ ID NO: 1), or a fragment thereof lacking only the N-terminal methionine, where the TadA* further contains a combination of amino acid alterations compared to the TadA*7.10 amino acid sequence selected from one or more of: i. Y123H, Y147R, and Q154R, ii. I76Y, Y133H, Y147R, and Q154R, iii. V82S, and Q164R, iv. I76Y, V82S, Y123H, Y147R, and Q154R, v. I76Y, V82T, Y123H, Y147R, and Q154R, and vi. I76Y, V82T, Y123H, Y147T, and Q154S. In (c) the one or more guide polynucleotides contain a nucleic acid sequence selected from CCUCAGAUGUCUAUGUGUUU (SEQ ID NO: 1524), UGCUUACAAUGACUGAGAUCU (SEQ ID NO: 1535), UUGCUCUCCCAUGGCGUUGGA (SEQ ID NO: 3476), CCCC AUGGCGUUGGAAGGCA (SEQ ID NO: 3443), and UGCUCUCCCAUGGCGUUGGAA (SEQ ID NO: 3467) or containing at least 10-23 contiguous nucleotides of a spacer nucleic acid sequence listed in any one of Tables 2A to 2F. The method results in altering the nucleobase of the CFB polynucleotide.

In another aspect, the disclosure provides a method of altering a nucleobase of a complement factor B (CFB) polynucleotide. The method involves contacting the CFB polynucleotide with one or more guide polynucleotides, or one or more polynucleotides encoding the one or more guide polynucleotides, and a base editor containing a nucleic acid programmable DNA binding protein (napDNAbp) domain and a deaminase domain, or one or more polynucleotides encoding the base editor. The method involves (a) and (b) where in (a) the deaminase domain contains a cytidine deaminase or a TadA variant (TadA*)

containing an amino acid sequence having at least 90% sequence identity to the following TadA*7.10 amino acid sequence:

MSEVEFSHEYWMRHALTLAKRARDEREVPVGAVLVLNRRVIGEGWNRAIGLHDPTAHAEIMA
LRQGGLVMQNYRLIDATLYVTFEPCVMCAGAMIHSRIGRVVFGVRNAKTGAAGSLMDVLHYP

5 GMNHRVEITEGILADECAALLCYFFRMPRQVFNAQKKAQSSTD (SEQ ID NO: 1), or a fragment thereof lacking only the N-terminal methionine, where the TadA* further contains a combination of amino acid alterations compared to the TadA*7.10 amino acid sequence selected from one or more of: i. Y123H, Y147R, and Q154R, ii. I76Y, Y133H, Y147R, and Q154R, iii. V82S, and Q164R, iv. I76Y, V82S, Y123H, Y147R, and Q154R, v. I76Y, V82T,
10 Y123H, Y147R, and Q154R, and vi. I76Y, V82T, Y123H, Y147T, and Q154S. In (b) the one or more guide polynucleotides contains a spacer containing a nucleotide sequence selected from one or more of UGCUCCCCCAUGGCGUUGGAA (SEQ ID NO: 3467; gRNA3657), UUGCUCCCCCAUGGCGUUGGA (SEQ ID NO: 3476; gRNA3658), CCCC AUGGCGUUGGAAGGCA (SEQ ID NO: 3443; gRNA3660),
15 CCUCAGAUGUCUAUGUGUUU (SEQ ID NO: 1524; TSBTx3826), GCUUACAAUGACUGAGAUCU (SEQ ID NO: 1534; TSBTx3837), UGCUUACAAUGACUGAGAUCU (SEQ ID NO: 1535; TSBTx3837), and UCUCACCUCUGCAAGUAUUG (SEQ ID NO: 1529; TSBTx3835). The method results in altering the nucleobase of the CFB polynucleotide.

20 In another aspect, the disclosure provides a cell produced by the method of any aspect or embodiment of the disclosure.

In another aspect, the disclosure provides a base editor system containing a base editor containing 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
25 more guide polynucleotides, or one or more polynucleotides encoding the one or more guide polynucleotides. The one or more guide polynucleotides contain at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 contiguous nucleobases of a spacer containing a nucleotide sequence selected from CCUCAGAUGUCUAUGUGUUU (SEQ ID NO: 1524), UGCUUACAAUGACUGAGAUCU (SEQ ID NO: 1535), UUGCUCCCCCAUGGCGUUGGA (SEQ ID
30 NO: 3476), CCCC AUGGCGUUGGAAGGCA (SEQ ID NO: 3443), and UGCUCCCCCAUGGCGUUGGAA (SEQ ID NO: 3467) and/or listed in Table 2A to 2F.

In another aspect, the disclosure provides a polynucleotide encoding the base editor system of any aspect or embodiment of the disclosure, or a component thereof.

In another aspect, the disclosure provides a vector containing the base editor system or the polynucleotide of any aspect or embodiment of the disclosure.

In another aspect, the disclosure provides a lipid nanoparticle containing the base editor system or the polynucleotide of any aspect or embodiment of the disclosure.

5 In another aspect, the disclosure provides a lipid nanoparticle containing A) a polynucleotide encoding a base editor and B) a guide RNA, or a polynucleotide encoding a guide RNA.

In another aspect, the disclosure provides a pharmaceutical composition containing an effective amount of the base editor system, the polynucleotide, the vector, or the lipid
10 nanoparticle of any aspect or embodiment of the disclosure, and a pharmaceutically acceptable excipient.

In another aspect, the disclosure provides a kit containing the base editor system, the vector, the lipid nanoparticle, or the pharmaceutical composition of any aspect or embodiment of the disclosure, disposed within a container.

15 In another aspect, the disclosure provides a guide polynucleotide containing a sequence listed in any one of Tables 1A to 2F.

In another aspect, the disclosure provides a base editor system containing a base editor containing 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
20 more guide polynucleotides, or one or more polynucleotides encoding the one or more guide polynucleotides. The method involves (a), (b), (c), and (d), where in (a) the deaminase domain is a cytidine deaminase or contains a TadA variant (TadA*) containing an amino acid sequence having at least 90% sequence identity to the following TadA*7.10 amino acid sequence:

25 MSEVEFSHEYWMRHALTLAKRARDEREVPVGAVLVLNRRVIGEGWNRAIGLHDPTAHAEIMA
LRQGGLVMQNYRLIDATLYVTFEPCVMCAGAMIHSRIGRVVFGVRNAKTGAAGSLMDVLHYP
GMNHRVEITEGILADECAALLCYFFRMPRQVFNAQKKAQSSTD (SEQ ID NO: 1), or a
fragment thereof lacking only the N-terminal methionine, where the TadA* further contains a
combination of amino acid alterations compared to the TadA*7.10 amino acid sequence
30 selected from one or more of: i. Y123H, Y147R, and Q154R, ii. I76Y, Y133H, Y147R, and
Q154R, iii. V82S, and Q164R, iv. I76Y, V82S, Y123H, Y147R, and Q154R, v. I76Y, V82T,
Y123H, Y147R, and Q154R, and vi. I76Y, V82T, Y123H, Y147T, and Q154S. In (b) the one
or more guide polynucleotides contain a spacer containing a nucleotide sequence selected

from one or more of: UGCUCCCCAUGGCGUUGGAA (SEQ ID NO: 3467; gRNA3657),

UUGCUCCCCAUGGCGUUGGA (SEQ ID NO: 3476; gRNA3658),

CCCCAUGGCGUUGGAAGGCA (SEQ ID NO: 3443; gRNA3660),

CCUCAGAUGUCUAUGUGUUU (SEQ ID NO: 1524; TSBTx3826),

5 GCUUACAAUGACUGAGAUCU (SEQ ID NO: 1534; TSBTx3837),

UGC UUACAAUGACUGAGAUCU (SEQ ID NO: 1535; TSBTx3837), and

UCUCACCUCUGCAAGUAUUG (SEQ ID NO: 1529; TSBTx3835). In (c) the one or more

guide polynucleotides contain a sequence selected from one or more of:

End-mod SpCas9 guide polynucleotide

10 mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCU

AGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU (SEQ ID NO:

440),

HM01:

mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUAGAmGmCmUmAmGmAmAmUmAmGmCAAGU

15 UAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmG

mAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NO: 440), and

NLS (bpsv40):

mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCU

AGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsmU-NHC6-CrossL-

20 ac- CKRTADGSEFESPKKKRKV (SEQ ID NOs: 440 and 446),

where “N” represents any nucleotide, “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), and where the number of N nucleotides is between 15

and 25. In (d) the napDNAbp is an spCas9 nickase polypeptide that binds a protospacer

25 adjacent motif (PAM) selected from one or more of NGA, NGC, and NGG, where “N” is any

nucleotide.

In another aspect, the disclosure provides a lipid nanoparticle containing the base editor system or component thereof of any aspect or embodiment of the disclosure.

In another aspect, the disclosure provides a composition containing a polynucleotide
30 and a guide RNA. The polynucleotide encodes a base editor containing a nucleic acid programmable DNA binding protein (napDNAbp) domain and a deaminase domain. The deaminase domain is a cytidine deaminase or contains a TadA variant (TadA*) containing an amino acid sequence having at least 90% sequence identity to the following TadA*7.10

amino acid sequence:

MSEVEFSHEYWMRHALTLAKRARDEREVPVGAVLVNLRVIGEGWNRAIGLHDPTAHAEIMA
LRQGGLVMQNYRLIDATLYVTFEPCVMCAGAMIHSRIGRVVFGVRNAKTGAAGSLMDVLHYP
GMNHRVEITEGILADECAALLCYFFRMPRQVFNAQKKAQSSTD (SEQ ID NO: 1). The

- 5 TadA* further contains a combination of amino acid alterations compared to the TadA*7.10 amino acid sequence selected from one or more of: i. I76Y, V82T, Y123H, Y147T, and Q154S, ii. Y123H, Y147R, and Q154R, iii. I76Y, Y133H, Y147R, and Q154R, iv. V82S, and Q164R, v. I76Y, V82S, Y123H, Y147R, and Q154R, and vi. I76Y, V82T, Y123H, Y147R, and Q154R. The guide RNA contains a spacer containing a nucleotide sequence selected
- 10 from one or more of: CCUCAGAUGUCUAUGUGUUU (SEQ ID NO: 1524; TSBTx3826), UGCUCUCCCAUGGCGUUGGAA (SEQ ID NO: 3467; gRNA3657), UUGCUCUCCCAUGGCGUUGGA (SEQ ID NO: 3476; gRNA3658), CCCCAUGGCGUUGGAAGGCA (SEQ ID NO: 3443; gRNA3660), GCUUACAAUGACUGAGAUCU (SEQ ID NO: 1534; TSBTx3837),
- 15 UGCUUACAAUGACUGAGAUCU (SEQ ID NO: 1535; TSBTx3837), and UCUCACCUCUGCAAGUAUUG (SEQ ID NO: 1529; TSBTx3835) and/or containing at least 10-23 contiguous nucleotides of a spacer nucleic acid sequence listed in any one of Tables 2A to 2F.

- In another aspect, the disclosure provides a lipid nanoparticle (LNP) composition
- 20 containing an mRNA and a guide RNA. The mRNA encodes a base editor containing a nucleic acid programmable DNA binding protein (napDNAbp) domain and a deaminase domain. The deaminase domain is a cytidine deaminase or contains a TadA variant (TadA*) containing an amino acid sequence having at least 90% sequence identity to the following TadA*7.10 amino acid sequence:
- 25 MSEVEFSHEYWMRHALTLAKRARDEREVPVGAVLVNLRVIGEGWNRAIGLHDPTAHAEIMA
LRQGGLVMQNYRLIDATLYVTFEPCVMCAGAMIHSRIGRVVFGVRNAKTGAAGSLMDVLHYP
GMNHRVEITEGILADECAALLCYFFRMPRQVFNAQKKAQSSTD (SEQ ID NO: 1). The
- TadA* further contains a combination of amino acid alterations compared to the TadA*7.10 amino acid sequence selected from one or more of: i. I76Y, V82T, Y123H, Y147T, and
- 30 Q154S, ii. Y123H, Y147R, and Q154R, iii. I76Y, Y133H, Y147R, and Q154R, iv. V82S, and Q164R, v. I76Y, V82S, Y123H, Y147R, and Q154R, and vi. I76Y, V82T, Y123H, Y147R, and Q154R. The guide RNA contains a spacer containing a nucleotide sequence selected from one or more of: CCUCAGAUGUCUAUGUGUUU (SEQ ID NO: 1524; TSBTx3826),

UGCUCUCCCAUGGCGUUGGAA (SEQ ID NO: 3467; gRNA3657),
 UUGCUCUCCCAUGGCGUUGGA (SEQ ID NO: 3476; gRNA3658),
 CCCC AUGGCGUUGGAAGGCA (SEQ ID NO: 3443; gRNA3660),
 GCUUACAAUGACUGAGAUCU (SEQ ID NO: 1534; TSBTx3837),
 5 UGCUUACAAUGACUGAGAUCU (SEQ ID NO: 1535; TSBTx3837), and
 UCUCACCUCUGCAAGUAUUG (SEQ ID NO: 1529; TSBTx3835) and/or contains at least 10-
 23 contiguous nucleotides of a spacer nucleic acid sequence listed in any one of Tables 2A to
 2F.

In another aspect, the disclosure provides a method of treatment involving
 10 administering to a subject a lipid nanoparticle (LNP) compositing containing an mRNA and a
 guide RNA. The mRNA encodes a base editor containing a nucleic acid programmable DNA
 binding protein (napDNAbp) domain and a deaminase domain. The deaminase domain is a
 cytidine deaminase or contains a TadA variant (TadA*) containing an amino acid sequence
 having at least 90% sequence identity to the following TadA*7.10 amino acid sequence:
 15 MSEVEFSHEYWMRHALTLAKRARDEREVPVGAVLVLNRRVIGEGWNRAIGLHDPTAHAEIMA
 LRQGGLVMQNYRLIDATLYVTFEPCVMCAGAMIHSRIGRVVFGVRNAKTGAAGSLMDVLHYP
 GMNHRVEITEGILADECAALLCYFFRMPRQVFNAQKKAQSSSTD (SEQ ID NO: 1). The
 TadA* further contains a combination of amino acid alterations compared to the TadA*7.10
 amino acid sequence selected from one or more of: i. I76Y, V82T, Y123H, Y147T, and
 20 Q154S, ii. Y123H, Y147R, and Q154R, iii. I76Y, Y133H, Y147R, and Q154R, iv. V82S, and
 Q164R, v. I76Y, V82S, Y123H, Y147R, and Q154R, and vi. I76Y, V82T, Y123H, Y147R,
 and Q154R. The guide RNA contains a spacer containing a nucleotide sequence selected
 from one or more of: CCUCAGAUGUCUAUGUGUUU (SEQ ID NO: 1524; TSBTx3826),
 UGCUCUCCCAUGGCGUUGGAA (SEQ ID NO: 3467; gRNA3657),
 25 UUGCUCUCCCAUGGCGUUGGA (SEQ ID NO: 3476; gRNA3658),
 CCCC AUGGCGUUGGAAGGCA (SEQ ID NO: 3443; gRNA3660),
 GCUUACAAUGACUGAGAUCU (SEQ ID NO: 1534; TSBTx3837),
 UGCUUACAAUGACUGAGAUCU (SEQ ID NO: 1535; TSBTx3837), and
 UCUCACCUCUGCAAGUAUUG (SEQ ID NO: 1529; TSBTx3835) and/or containing at least
 30 10-23 contiguous nucleotides of a spacer nucleic acid sequence listed in any one of Tables
 2A to 2F.

In any aspect or embodiment of the disclosure the splice site is located near the 3' end
 of Exon 1, Exon 10, Exon 11, Exon 12, Exon 14, Exon 15, or Exon 16 of the CFB

polynucleotide. In any aspect or embodiment of the disclosure, the splice site is located near the 5' end of Exon 5, Exon 8, Exon 9, Exon 10, Exon 11, Exon 14, or Exon 18 or the CFB polynucleotide.

In any aspect or embodiment of the disclosure, the one or more guide polynucleotides contain a spacer complementary to both a human CFB polynucleotide and a non-human primate CFB polynucleotide. In any aspect or embodiment of the disclosure, the one or more guide polynucleotides contains a spacer complementary to a human CFB polynucleotide but not to a non-human primate CFB polynucleotide. In any aspect or embodiment of the disclosure, the one or more guide polynucleotides contain a spacer containing only 20 or 21 nucleotides. In any aspect or embodiment of the disclosure, the one or more guide polynucleotides contain a spacer containing a nucleotide sequence selected from one or more of: UGCUCCCCAUGGCGUUGGAA (SEQ ID NO: 3467; gRNA3657), UUGCUCCCCAUGGCGUUGGA (SEQ ID NO: 3476; gRNA3658), CCCC AUGGCGUUGGAAGGCA (SEQ ID NO: 3443; gRNA3660), CCUCAGAUGUCUAUGUGUUU (SEQ ID NO: 1524; TSBTx3826), GCUUACAAUGACUGAGAUCU (SEQ ID NO: 1534; TSBTx3837), UGCUUACAAUGACUGAGAUCU (SEQ ID NO: 1535; TSBTx3837) and UCUCACCUCUGCAAGUAUUG (SEQ ID NO: 1529; TSBTx3835).

In any aspect or embodiment of the disclosure, the deaminase domain is an adenosine deaminase containing the TadA*7.10 amino acid sequence further containing a combination of amino acid alterations selected from one or more of: i. Y123H, Y147R, and Q154R, ii. I76Y, Y133H, Y147R, and Q154R, iii. V82S, and Q164R, iv. I76Y, V82S, Y123H, Y147R, and Q154R, v. I76Y, V82T, Y123H, Y147R, and Q154R, and vi. I76Y, V82T, Y123H, Y147T, and Q154S.

In any aspect or embodiment of the disclosure, the napDNAbp is a nickase. In any aspect or embodiment of the disclosure, the napDNAbp binds a protospacer adjacent motif (PAM) selected from one or more of NGA, NGC, NGG, and NNNRRT, where "N" is any nucleotide and "R" is A or G. In any aspect or embodiment of the disclosure, the napDNAbp is a Cas9 polypeptide.

In any aspect or embodiment of the disclosure, the one or more guide polynucleotides contain a modified nucleotide. In any aspect or embodiment of the disclosure, the one or more guide polynucleotides contain a sequence selected from one or more of: End-mod SpCas9 guide polynucleotide

mNsmNsmNsNNNNNNNNNNNNNNNNNNNGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCU
AGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU (SEQ ID NO:
440);

End-mod SaCas9 guide polynucleotide

5 mNsmNsmNsNNNNNNNNNNNNNNNNNNNGUUUUAGUACUCUGUAAUGAAAAUUACAGAAUCUA
CUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU
(SEQ ID NO: 3128);

HM01:

mNsmNsmNsNNNNNNNNNNNNNNNNNNNGUUUUAGAmGmCmUmAmGmAmAmUmAmGmCAAGU
10 UAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmG
mAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NO: 440);

HM07:

mNsmNsmNsmNmNmNmNmNmNmNmNNNNNNNNNNNmGUUUUAGmAmGmCmUmAmGmAmAmUm
AmGmCmAmAGUUmAAmAAmUAmAmGmGmCmUmAGUmCmCGUUmUmCAAmCmUmUmGmAmAm
15 AmAmAmGmUmGGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NO:
440);

NLS (bpsv40):

mNsmNsmNsNNNNNNNNNNNNNNNNNNNGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCU
AGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsmU-NHC6-CrossL-
20 ac- CKRTADGSEFESPKKKRKV (SEQ ID NOs: 440 and 446);

LONGEST:

mNsmNsmNsNNNNNNNNNNNNNNNNNNNGUUUUAGAmGmCmCmGmGmCmGmAmAmAmCmGmC
mCmGmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGUGmG
mCmAmCmCmGmAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NO: 445);

25 NLS + LONGEST:

mNsmNsmNsNNNNNNNNNNNNNNNNNNNGUUUUAGAmGmCmCmGmGmCmGmAmAmAmCmGmC
mCmGmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmG
mGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmUsmUsmUsmU-NHC5-CrossL-
CKRTADGSEFESPKKKRKV (SEQ ID NOs: 445 and 446); and

30 LONGEST + GOLD:

mNsmNsmNsNNNNNNNNNNNNNNNNNNNGUUUUAGAmGmCmCmGmGmCmGmAmAmAmCmGmC
mCmGmGmCAAGUUAAAAUAAGGCUAGUCCGUUAmUmCAAmCmUmUGGACUUCGGUCCmAmAm
GUGGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NO: 447);

where “N” represents any nucleotide, “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), and where the number of N nucleotides is between 15 and 25.

5 In any aspect or embodiment of the disclosure, the CFB polynucleotide is in a cell. In any aspect or embodiment of the disclosure, the cell is a mammalian cell. In any aspect or embodiment of the disclosure, the cell is a retinal cell or other cell of the eye, a nerve cell, or a hepatocyte.

In any aspect or embodiment of the disclosure, the one or more guide polynucleotides target the base editor to effect an alteration of the nucleobase of the CFB polynucleotide that disrupts a splice site in the CFB polynucleotide.

In any aspect or embodiment of the disclosure, the napDNAbp is a nickase.

In any aspect or embodiment of the disclosure, the napDNAbp binds a protospacer adjacent motif (PAM) selected from one or more of NGA, NGC, NGG, and NNNRRT, where
15 “N” is any nucleotide and “R” is A or G.

In any aspect or embodiment of the disclosure, the napDNAbp is a Cas9 polypeptide.

In any aspect or embodiment of the disclosure, CFB activity, protein concentration, and/or mRNA concentration is reduced by at least about 15% as compared to a control cell without the alteration.

20 In any aspect or embodiment of the disclosure, the CFB polynucleotide is contacted with two or more guide polynucleotides, and where each guide polynucleotide binds a different location within the CFB polynucleotide.

In any aspect or embodiment of the disclosure, the deaminase domain contains a cytidine deaminase or a TadA variant (TadA*) containing an amino acid sequence having at
25 least 90% sequence identity to the following TadA*7.10 amino acid sequence:

MSEVEFSHEYWMRHALTLAKRARDEREVPVGAFLVLNNRVIGEGWNRAIGLHDPTAHAEIMA
LRQGGLVMQNYRLIDATLYVTFEPCVMCAGAMIHSRIGRVVFGVRNAKTGAAGSLMDVLHYP
GMNHRVEITEGILADECAALLCYFFRMPRQVFNAQKKAQSSTD (SEQ ID NO: 1), where the
TadA* further contains a combination of amino acid alterations compared to the TadA*7.10
30 amino acid sequence selected from one or more of: i. Y123H, Y147R, and Q154R, ii. I76Y, Y133H, Y147R, and Q154R, iii. V82S, and Q164R, iv. I76Y, V82S, Y123H, Y147R, and Q154R, v. I76Y, V82T, Y123H, Y147R, and Q154R, and vi. I76Y, V82T, Y123H, Y147T, and Q154S.

In any aspect or embodiment of the disclosure, the method is not a process for modifying the germline genetic identity of human beings.

In any aspect or embodiment of the disclosure, the adenosine deaminase domain contains a combination of mutations selected from those listed in **Table 5G**.

- 5 In any aspect or embodiment of the disclosure, the guide RNA contains a sequence selected from one or more of:

End-mod SpCas9 guide polynucleotide

mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUUAGAGCUAGAAAUAGCAAGUAAAAUAAGGCU
AGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU (SEQ ID NO:

- 10 440),

HM01:

mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUUAGAmGmCmUmAmGmAmAmUmAmGmCAAGU
UAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmG
mAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NO: 440), and

- 15 NLS (bpsv40):

mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUUAGAGCUAGAAAUAGCAAGUAAAAUAAGGCU
AGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsmU-NHC6-CrossL-
ac- CKRTADGSEFESPKKKRKV (SEQ ID NOs: 440 and 446),

- 20 where “N” represents any nucleotide, “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), and where the number of N nucleotides is between 15 and 25.

In any aspect of the disclosure, or embodiments thereof, the polynucleotide is an mRNA.

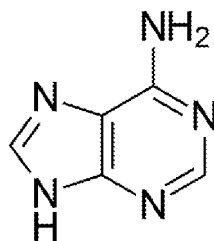
- 25 In any aspect of the disclosure, or embodiments thereof, the composition is formulated in a lipid nanoparticle (LNP).

Definitions

- 30 Unless defined otherwise, all technical and scientific terms used herein have the meaning commonly understood by a person skilled in the art to which this disclosure belongs. The following references provide one of skill with a general definition of many of the terms used in this disclosure: Singleton *et al.*, Dictionary of Microbiology and Molecular Biology (2nd ed. 1994); The Cambridge Dictionary of Science and Technology (Walker ed., 1988);

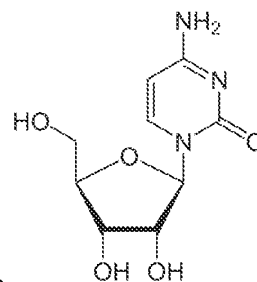
The Glossary of Genetics, 5th Ed., R. Rieger *et al.* (eds.), Springer Verlag (1991); and Hale & Marham, The Harper Collins Dictionary of Biology (1991). As used herein, the following terms have the meanings ascribed to them below, unless specified otherwise.

By “adenine” or “9*H*-Purin-6-amine” is meant a purine nucleobase with the



- 5 molecular formula $C_5H_5N_5$, having the structure , and corresponding to CAS No. 73-24-5.

By “adenosine” or “4-Amino-1-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]pyrimidin-2(1*H*)-one” is meant an adenine molecule attached to



- a ribose sugar via a glycosidic bond, having the structure , and
10 corresponding to CAS No. 65-46-3. Its molecular formula is $C_{10}H_{13}N_5O_4$.

- By “adenosine deaminase” or “adenine deaminase” is meant a polypeptide or fragment thereof capable of catalyzing the hydrolytic deamination of adenine or adenosine. In some embodiments, the deaminase or deaminase domain is an adenosine deaminase catalyzing the hydrolytic deamination of adenosine to inosine or deoxy adenosine to deoxyinosine. In some embodiments, the adenosine deaminase catalyzes the hydrolytic deamination of adenine or adenosine in deoxyribonucleic acid (DNA). The adenosine deaminases (*e.g.*, engineered adenosine deaminases, evolved adenosine deaminases) provided herein may be from any organism (*e.g.*, eukaryotic, prokaryotic), including but not limited to algae, bacteria, fungi, plants, invertebrates (*e.g.*, insects), and vertebrates (*e.g.*, amphibians,
15 mammals). In some embodiments, the adenosine deaminase is an adenosine deaminase variant with one or more alterations and is capable of deaminating both adenine and cytosine in a target polynucleotide (*e.g.*, DNA, RNA) and may be referred to as a “dual deaminase”. Non-limiting examples of dual deaminases include those described in PCT/US22/22050. In some embodiments, the target polynucleotide is single or double stranded. In some
20

embodiments, the adenosine deaminase variant is capable of deaminating both adenine and cytosine in DNA. In some embodiments, the adenosine deaminase variant is capable of deaminating both adenine and cytosine in single-stranded DNA. In some embodiments, the adenosine deaminase variant is capable of deaminating both adenine and cytosine in RNA. In

5 embodiments, the adenosine deaminase variant is selected from those described in PCT/US2020/018192, PCT/US2020/049975, PCT/US2017/045381, PCT/US2021/016827, PCT/US2022/073781, PCT/US24/34189, or PCT/US2020/028568, the full contents of which are each incorporated herein by reference in their entireties for all purposes. Further non-limiting examples of adenosine deaminases include those disclosed or referenced in Rufflow,

10 *et al.*, “Design of highly functional genome editors by modeling of the universe of CRISPR-Cas Sequences,” *bioRxiv*, posted April 22, 2024, doi: 10.1101/2024.04.22.590591, the disclosure of which is incorporated herein by reference in its entirety for all purposes, which were designed using artificial intelligence. Further exemplary adenosine deaminase amino acid sequences include: TadA-8e (SEQ ID NO: 3575), Tad1 (SEQ ID NO: 3576), Tad2 (SEQ

15 ID NO: 3577), Tad3 (SEQ ID NO: 3578), Tad4 (SEQ ID NO: 3579), Tad6 (SEQ ID NO: 3580), Tad6-SR (SEQ ID NO: 3581), TadA9 (SEQ ID NO: 3582), TadA20 (SEQ ID NO: 3583), *Staphylococcus aureus* TadA (SEQ ID NO: 3584), *Bacillus subtilis* TadA (SEQ ID NO: 3585), *Salmonella typhimurium* TadA (SEQ ID NO: 3586), *Shewanella putrefaciens* (SEQ ID NO: 3587), *Haemophilus influenzae* F3031 TadA (SEQ ID NO: 3588), *Caulobacter*

20 *crescentus* TadA (SEQ ID NO: 3589), *Geobacter sulfurreducens* TadA (SEQ ID NO: 3590), *Streptococcus pyogenes* TadA (SEQ ID NO: 3591), *Aquifex aeolicus* TadA (SEQ ID NO: 3592), and *E. coli* TadA deaminase (ecTadA) (SEQ ID NO: 3593).

By “adenosine deaminase activity” is meant catalyzing the deamination of adenine or adenosine to guanine in a polynucleotide.

25 By “Adenosine Base Editor (ABE)” is meant a base editor comprising an adenosine deaminase.

By “Adenosine Base Editor (ABE) polynucleotide” is meant a polynucleotide encoding an ABE.

By “Adenosine Base Editor 8 (ABE8) polypeptide” or “ABE8” is meant a base editor

30 as defined herein comprising an adenosine deaminase or adenosine deaminase variant comprising one or more of the alterations listed in **Table 5B**, one of the combinations of alterations listed in **Table 5B**, or an alteration at one or more of the amino acid positions listed in **Table 5B**, where such alterations are relative to the following reference sequence: MSEVEFSHEYWMRHALTLAKRRADEREVPVGAVLVLNRRVIGEGWNRAIGLHDPTAHAEIMA

LRQGGLVMQNYRLIDATLYVTFEPCVMCAGAMIHSRIGRVVFGVRNAKTGAAGSLMDVLHYP
GMNHRVEITEGILADECAALLCYFFRMPRQVFNAQKKAQSSTD (SEQ ID NO: 1), or a

corresponding position in another adenosine deaminase. In embodiments, ABE8 comprises alterations at amino acids 82 and/or 166 of SEQ ID NO: 1. In some embodiments, ABE8
5 comprises further alterations, as described herein, relative to the reference sequence.

By “Adenosine Base Editor 8 (ABE8) polynucleotide” is meant a polynucleotide encoding an ABE8 polypeptide.

“Administering” is referred to herein as providing one or more compositions described herein to a patient or a subject. By way of example and without limitation,
10 composition administration (e.g., injection) can be performed by intravenous (i.v.) injection, sub-cutaneous (s.c.) injection, intradermal (i.d.) injection, intraperitoneal (i.p.) injection, or intramuscular (i.m.) injection. One or more such routes can be employed. Parenteral administration can be, for example, by bolus injection or by gradual perfusion over time. In some embodiments, parenteral administration includes infusing or injecting intravascularly,
15 intravenously, intramuscularly, intraarterially, intrathecally, intratumorally, intradermally, intraperitoneally, transtracheally, subcutaneously, subcuticularly, intraarticularly, subcapsularly, subarachnoidly and intrasternally. Alternatively, or concurrently, administration can be by the oral route.

By “agent” is meant any small molecule chemical compound, antibody, nucleic acid
20 molecule, polypeptide, or functional fragments thereof.

By “alteration” is meant a change in the level, structure, or activity of an analyte, gene or polypeptide as detected by standard art known methods such as those described herein. As used herein, an alteration includes a change (e.g., increase or reduction) in expression levels. In embodiments, the increase or reduction in expression levels is by 10%, 25%, 40%, 50% or
25 greater. In some embodiments, an alteration includes an insertion, deletion, or substitution of a nucleobase or amino acid (by, e.g., genetic engineering).

By “ameliorate” is meant reduce, suppress, attenuate, diminish, arrest, or stabilize the development or progression of a disease.

By “analog” is meant a molecule that is not identical but has analogous functional or
30 structural features. For example, a polypeptide analog retains the biological activity of a corresponding naturally-occurring polypeptide, while having certain biochemical modifications that enhance the analog’s function relative to a naturally occurring polypeptide. Such biochemical modifications could increase the analog’s protease resistance, membrane

permeability, or half-life, without altering, for example, ligand binding. An analog may include an unnatural amino acid.

By “base editor (BE),” or “nucleobase editor polypeptide (NBE)” is meant an agent that binds a polynucleotide and has nucleobase modifying activity. In various embodiments, the base editor comprises a nucleobase modifying polypeptide (*e.g.*, a deaminase) and a polynucleotide programmable nucleotide binding domain (*e.g.*, Cas9 or Cpf1).

Representative nucleic acid and protein sequences of base editors include those sequences having about or at least about 85% sequence identity to any base editor sequence provided in the sequence listing, such as those corresponding to SEQ ID NOs: 2-11.

By “BE4 cytidine deaminase (BE4) polypeptide,” is meant a base editor comprising a nucleic acid programmable DNA binding protein (napDNAbp) domain, a cytidine deaminase domain, and two uracil glycosylase inhibitor domains (UGIs). In embodiments, the napDNAbp is a Cas9n (D10A) polypeptide. Non-limiting examples of cytidine deaminase domains include rAPOBEC, ppAPOBEC, RrA3F, AmAPOBEC1, and SsAPOBEC3B.

By “BE4 cytidine deaminase (BE4) polynucleotide,” is meant a polynucleotide encoding a BE4 polypeptide.

By “base editing activity” is meant acting to chemically alter a base within a polynucleotide. In one embodiment, a first base is converted to a second base. In one embodiment, the base editing activity is cytidine deaminase activity, *e.g.*, converting target C•G to T•A. In another embodiment, the base editing activity is adenosine or adenine deaminase activity, *e.g.*, converting A•T to G•C.

The term “base editor system” refers to an intermolecular complex for editing a nucleobase of a target nucleotide sequence. In various embodiments, the base editor (BE) system comprises (1) a polynucleotide programmable nucleotide binding domain, a deaminase domain (*e.g.*, cytidine deaminase or adenosine deaminase) for deaminating nucleobases in the target nucleotide sequence; and (2) one or more guide polynucleotides (*e.g.*, guide RNA) in conjunction with the polynucleotide programmable nucleotide binding domain. In various embodiments, the base editor (BE) system comprises a nucleobase editor domain selected from an adenosine deaminase or a cytidine deaminase, and a domain having nucleic acid sequence specific binding activity. In some embodiments, the base editor system comprises (1) a base editor (BE) comprising a polynucleotide programmable DNA binding domain and a deaminase domain for deaminating one or more nucleobases in a target nucleotide sequence; and (2) one or more guide RNAs in conjunction with the polynucleotide programmable DNA binding domain. In some embodiments, the polynucleotide

programmable nucleotide binding domain is a polynucleotide programmable DNA binding domain. In some embodiments, the base editor is a cytidine base editor (CBE). In some embodiments, the base editor is an adenine or adenosine base editor (ABE). In some embodiments, the base editor is an adenine or adenosine base editor (ABE) or a cytidine or cytosine base editor (CBE). In some embodiments, the base editor system (e.g., a base editor system comprising a cytidine deaminase) comprises a uracil glycosylase inhibitor or other agent or peptide (e.g., a uracil stabilizing protein such as provided in WO2022015969, the disclosure of which is incorporated herein by reference in its entirety for all purposes) that inhibits the inosine base excision repair system.

The term “Cas9” or “Cas9 domain” refers to an RNA guided nuclease comprising a Cas9 protein, or a fragment thereof (e.g., a protein comprising an active, inactive, or partially active DNA cleavage domain of Cas9, and/or the gRNA binding domain of Cas9). A Cas9 nuclease is also referred to sometimes as a casnl nuclease or a CRISPR (clustered regularly interspaced short palindromic repeat) associated nuclease.

The term “conservative amino acid substitution” or “conservative mutation” refers to the replacement of one amino acid by another amino acid with a common property. A functional way to define common properties between individual amino acids is to analyze the normalized frequencies of amino acid changes between corresponding proteins of homologous organisms (Schulz, G. E. and Schirmer, R. H., Principles of Protein Structure, Springer-Verlag, New York (1979)). According to such analyses, groups of amino acids can be defined where amino acids within a group exchange preferentially with each other, and therefore resemble each other most in their impact on the overall protein structure (Schulz, G. E. and Schirmer, R. H., *supra*). Non-limiting examples of conservative mutations include amino acid substitutions of amino acids, for example, lysine for arginine and vice versa such that a positive charge can be maintained; glutamic acid for aspartic acid and vice versa such that a negative charge can be maintained; serine for threonine such that a free –OH can be maintained; and glutamine for asparagine such that a free –NH₂ can be maintained.

Amino acids generally can be grouped into classes according to the following common side- chain properties:

- (1) hydrophobic: Norleucine, Met, Ala, Val, Leu, Ile;
- (2) neutral hydrophilic: Cys, Ser, Thr, Asn, Gln;
- (3) acidic: Asp, Glu;
- (4) basic: His, Lys, Arg;
- (5) residues that influence chain orientation: Gly, Pro;

(6) aromatic: Trp, Tyr, Phe.

In some embodiments, conservative substitutions can involve the exchange of a member of one of these classes for another member of the same class. In some embodiments, non-conservative amino acid substitutions can involve exchanging a member of one of these classes for another class.

The term “coding sequence” or “protein coding sequence” as used interchangeably herein refers to a segment of a polynucleotide that codes for a protein. Coding sequences can also be referred to as open reading frames. The region or sequence is bounded nearer the 5' end by a start codon and nearer the 3' end with a stop codon. Stop codons useful with the base editors described herein include the following: TAG, TAA, and TGA.

By “complement factor B (CFB) polypeptide” or “factor B (FB) polypeptide” is meant a factor B protein with at least about 85% amino acid sequence identity to GenBank Accession No. AAA16820.1, which is provided below, or a fragment thereof that is capable of mediating activation of the complement system. In embodiments, CFB is capable of cleaving an Arg-Ser bond in complement component C3 to yield C3a and C3b and/or an Arg-Ser bond in complement component C5 to yield C5a and C5b.

>AAA16820.1 complement factor B [Homo sapiens]

MGSNLSPQLCLMPFILGLLSGGVTTTPWSLAQPQGSCLLEGVEIKGGSFRLLQEGQALEYVC
PSGFYPYPVQTRTCRSTGWSSTLKTQDQKTVRKAECRAIHCPRPHDFENGEYWPRSPYYNVS
DEISFHCYDGYTLRGSANRTCQVNGRWSGQTAICDNGAGYCSNPGIPIGTRKVGVSQYRLEDS
VTYHCSRGLTLRGSQRRTCQEGGSWSGTEPSCQDSFMYDTPQEVAAFLSSLTETIEGVDAE
DGHGPGEQQKRKIVLDPSGSMNIYLVLDGSDSIGASNFTGAKKCLVNLIKVASYGVKPRYG
LVTYATYPKIWVKVSEADSSNADWVTQQLNEINYEDHKLKSGTNTKKALQAVYSMMSPDDV
PPEGWNRTRHVIILMTDGLHNMGGDPITVIDEIRDLLYIGKDRKNPREDYLDVYVFGVGPLV
NQVNINALASKKDNEQHVFKVKDMENLEDVIFYQMIDESQSLSLCGMVWEHRKGTDYHKQPWQ
AKISVIRPSKGHESCMGAVVSEYFVLTAACHCFTVDDKEHSIKVSVGGEKRDLEIEVVLFHPN
YNINGKKEAGIPEFYDYDVALIKLKNKLKYGQTIRPICLPCTEGTTRALRLPPTTTCQQQKE
ELLPAQDIKALFVSEEEKLTRKEVYIKNGDKKGCERDAQYAPGYDKVKDISEVVTPRFLC
TGGVSPYADPNTCRGDSGGPLIVHKRSRFIQVGVISWGVVDVCKNQKRQKQVPAHARDFHIN
LFQVLPWLKEKLQDEDLGFL (SEQ ID NO: 426)

By “complement factor B (CFB) polynucleotide” or “factor B (FB) polynucleotide” is meant a nucleic acid molecule encoding a CFB polypeptide, as well as the introns, exons, 3' untranslated regions, 5' untranslated regions, and regulatory sequences associated with its expression, or fragments thereof. In embodiments, a CFB polynucleotide is the genomic

sequence, cDNA, mRNA, or gene associated with and/or required for CFB expression. An exemplary CFB nucleotide sequences from *Homo Sapiens* is provided below (GenBank: L15702.1:41-2335; Ensembl: ENST00000425368.7):

>L15702.1:41-2335 Human complement factor B mRNA, complete cds

```

5  ATGGGGAGCAATCTCAGCCCCCACTCTGCCTGATGCCCTTTATCTTGGGCCTCTTGCTCTGG
   AGGTGTGACCACCACTCCATGGTCTTTGGCCCAGCCCCAGGGATCCTGCTCTCTGGAGGGGG
   TAGAGATCAAAGGCGGCTCCTTCCGACTTCTCCAAGAGGGCCAGGCACTGGAGTACGTGTGT
   CCTTCTGGCTTCTACCCGTACCCTGTGCAGACACGTACCTGCAGATCTACGGGGTCTCTGGAG
   CACCCTGAAGACTCAAGACCAAAAGACTGTCAGGAAGGCAGAGTGCAGAGCAATCCACTGTCT
10  CAAGACCACACGACTTCGAGAACGGGGAATACTGGCCCCGGTCTCCCTACTACAATGTGAGT
   GATGAGATCTCTTTCCACTGCTATGACGGTTACACTCTCCGGGGCTCTGCCAATCGCACCTG
   CCAAGTGAATGGCCGGTGGAGTGGGCAGACAGCGATCTGTGACAACGGAGCGGGGTACTGCT
   CCAACCCGGGCATCCCCATTGGCACAAGGAAGGTGGGCAGCCAGTACCGCCTTGAAGACAGC
   GTCACCTACCACTGCAGCCGGGGGCTTACCCTGCGTGGCTCCCAGCGGCGAACGTGTCAGGA
15  AGGTGGCTCTTGGAGCGGGACGGAGCCTTCCTGCCAAGACTCCTTCATGTACGACACCCCTC
   AAGAGGTGGCCGAAGCTTTCCTGTCTTCCCTGACAGAGACCATAGAAGGAGTCGATGCTGAG
   GATGGGCACGGCCCAGGGGAACAACAGAAGCGGAAGATCGTCCTGGACCCTTCAGGCTCCAT
   GAACATCTACCTGGTGCTAGATGGATCAGACAGCATTGGGGCCAGCAACTTCACAGGAGCCA
   AAAAGTGTCTAGTCAACTTAATTGAGAAGGTGGCAAGTTATGGTGTGAAGCCAAGATATGGT
20  CTAGTGACATATGCCACATACCCCCAAAATTTGGGTCAAAGTGTCTGAAGCAGACAGCAGTAA
   TGCAGACTGGGTACGAAGCAGCTCAATGAAATCAATTATGAAGACCACAAGTTGAAGTCAG
   GGACTAACACCAAGAAGGCCCTCCAGGCAGTGTACAGCATGATGAGCTGGCCAGATGACGTC
   CCTCTGAAGGCTGGAACCGCACCCGCCATGTCATCATCCTCATGACTGATGGATTGCACAA
   CATGGGCGGGGACCCAATTACTGTCAATTGATGAGATCCGGGACTTGCTATACATTGGCAAGG
25  ATCGCAAAAACCAAGGGAGGATTATCTGGATGTCTATGTGTTTGGGGTCGGGCCTTTGGTG
   AACCAAGTGAACATCAATGCTTTGGCTTCCAAGAAAGACAATGAGCAACATGTGTTCAAAGT
   CAAGGATATGGAAAACCTGGAAGATGTTTTCTACCAAATGATCGATGAAAGCCAGTCTCTGA
   GTCTCTGTGGCATGGTTTGGGAACACAGGAAGGGTACCGATTACCACAAGCAACCATGGCAG
   GCCAAGATCTCAGTCATTCGCCCTTCAAAGGGACACGAGAGCTGTATGGGGGCTGTGGTGTC
30  TGAGTACTTTGTGCTGACAGCAGCACATTGTTTCACTGTGGATGACAAGGAACACTCAATCA
   AGGTGAGCGTAGGAGGGGAGAAGCGGGACCTGGAGATAGAAGTAGTCCTATTTTACCCCAAC
   TACAACATTAATGGGAAAAAAGAAGCAGGAATTCCTGAATTTTATGACTATGACGTTGCCCT
   GATCAAGCTCAAGAATAAGCTGAAATATGGCCAGACTATCAGGCCCATTTGTCTCCCTGCA
   CCGAGGGAACAACCTCGAGCTTTGAGGCTTCCTCCAACCTACCACTTGCCAGCAACAAAAGGAA

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GAGCTGCTCCCTGCACAGGATATCAAAGCTCTGTTTGTGTCTGAGGAGGAGAAAAAGCTGAC
 TCGGAAGGAGGTCTACATCAAGAATGGGGATAAGAAAGGCAGCTGTGAGAGAGATGCTCAAT
 ATGCCCCAGGCTATGACAAAGTCAAGGACATCTCAGAGGTGGTCACCCCTCGGTTCCCTTTGT
 ACTGGAGGAGTGAGTCCCTATGCTGACCCCAATACTTGACAGAGGTGATTCTGGCGGCCCTT
 5 GATAGTTCACAAGAGAAGTCGTTTCATTCAAGTTGGTGTAATCAGCTGGGGAGTAGTGGATG
 TCTGCAAAAACCAGAAGCGGCAAAAGCAGGTACCTGCTCACGCCCCGAGACTTTCACATCAAC
 CTCTTTCAAGTGCTGCCCTGGCTGAAGGAGAACTCCAAGATGAGGATTTGGGTTTTCTATA
 A (SEQ ID NO: 427)

>chromosome:GRCh38:6:31945050:31952686:1 (ENST00000425368.7), where exons are
 10 shown in **bold text**, untranslated regions are underlined, introns correspond to plain text
 regions between **bold text** regions, and a TATA box is shown by double-underlined text. The
 sequence contains 18 exons, where Exon 1 corresponds to the first exon from the 5' end of
 the sequence, Exon 2 corresponds to the second exon from the 5' end of the sequence, and so
 on to Exon 18.

15 AGGACCCAGGGGTTACAGGATCTCAGCCTTGTGGGGGGATGAGGGAGGCCTTTGAGGGATC
 TAGGGAGGTTGGGGCTTACAGTTGGGGCTGTGGCAGCCTCCAGCCAGTTCTCTCCTTTTCT
 CCAGGTGGGTCTGGTGAGCTGGGGCTTTACAACCCCTGCCTTGGCTCTGCTGACAAAACT
 CCCGCAAAAGGGCCCCCTCGTAGCAAGGTCCCGCCGCCACGAGACTTTCACATCAATCTCTTC
 CGCATGCAGCCCTGGCTGAGGCAGCACCTGGGGGATGTCCTGAATTTTTTACCCCTCTAGCC
 20 ATGGCCACTGAGCCCTCTGCTGCCCTGCCAGAATCTGCCGCCCCCTCCATCTTCTACCTCTGA
 ATGGCCACCCTTAGACCCTGTGATCCATCCTCTCTCTAGCTGAGTAAATCCGGGTCTCTAG
 GATGCCAGAGGCAGCGCACACAAGCTGGGAAATCCTCAGGGCTCCTACCAGCAGGACTGCCT
 CGCTGCCCCACCTCCCGCTCCTTGGCCTGTCCCCAGATTCTTCCCTGGTTGACTTGACTCA
 TGCTTGTTTTCACTTTCACATGGAATTTCCAGTTATGAAATTAATAAAAATCAATGGTTTCC
 25 ACATCTCTCAGTGCCTCTATCTGGAGGCCAGGTAGGGCTGGCCTTGGGGGAGGGGGAGGCCA
 GAATGACTCCAAGAGCTACAGGAAGGCAGGTGAGAGACCCCACTGGACAAACAGTGGCTGGA
 CTCTGCACCATAACACACAATCAACAGGGGAGTGAGCTGGATCCTTATTTCTGGTCCCTAAG
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 30 AGCGGGGCCCTCCCGCTTGGATGTTCCGGGAAAGTGATGTGGGTAGGACAGGCGGGGCGAGC
 CGCAGGTGCCAGAACACAGATTGTATAAAAGGCTGGGGGCTGGTGGGGAGCAG**GGGAAGGGA**
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5 GATCTACGGGGTCTGGAGCACCTGAAGACTCAAGACCAAAAAGACTGTCAGGAAGGCAGAG
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10 GCAGTGGAAATCCATATGGGTTGAGGAGTAGGTAAGATGCTGCTTCTGCGGGACTGGGAATG
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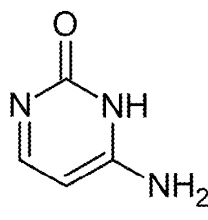
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TACCTTGAGGGCGACAGGGAGGACCACTTTGTAGTCAAAAGTTGAACAGCAGGATCGTTGGG
5 CAATGGAGGTTAGTGGGAACCTGTTGGGGGCTGGAAGGGCCACTTTGTGGTCAAAGGGAAGT
CCGTGTAATGATGATTAACTTAAAAAGTTGAAAGATGTGGGATTTCAAGTTCAGATTGGTCT
CTGGGGTTAAAAAGATGGCTTGGAAGACCAGGTGAGGTGATGGTCTCTTCCCTCTCCACAGAC
CACAAGTTGAAGTCAGGGACTAACACCAAGAAGGCCCTCCAGGCAGTGTACAGCATGATGAG
CTGGCCAGATGACGTCCCTCCTGAAGGCTGGAACCGCACCCGCCATGTCATCATCTCATGA
10 CTGATGGTCAGAAGGGACCTCTCTCCTGTCCCAGCCTCCCCACCTTCTCAGACCAGCATGTG
GCCCTTAAGTCCACTTGTAACACTATACCCATGGTTGGGGCCCTGAATGTGACTCATAGCTG
GCTGTTTCATCTCTCCTGTGACCCTTCATAAGGAATTCTTCTTAAGCCCTGTGATCAACTATC
TCTAACCCCTTCCTCAACTTGCTCACCCCTGCCATGTGTATCCCTGCCTTTAGCCAGTTTATCT
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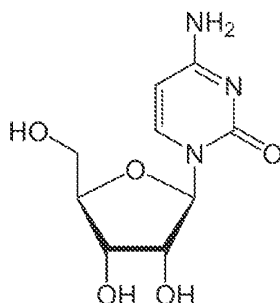
By “complex” is meant a combination of two or more molecules whose interaction relies on inter-molecular forces. Non-limiting examples of inter-molecular forces include covalent and non-covalent interactions. Non-limiting examples of non-covalent interactions include hydrogen bonding, ionic bonding, halogen bonding, hydrophobic bonding, van der Waals interactions (e.g., dipole-dipole interactions, dipole-induced dipole interactions, and London dispersion forces), and π -effects. In an embodiment, a complex comprises polypeptides, polynucleotides, or a combination of one or more polypeptides and one or more polynucleotides. In one embodiment, a complex comprises one or more polypeptides that associate to form a base editor (e.g., base editor comprising a nucleic acid programmable DNA binding protein, such as Cas9, and a deaminase) and a polynucleotide (e.g., a guide RNA). In an embodiment, the complex is held together by hydrogen bonds. It should be appreciated that one or more components of a base editor (e.g., a deaminase, or a nucleic acid programmable DNA binding protein) may associate covalently or non-covalently. As one example, a base editor may include a deaminase covalently linked to a nucleic acid programmable DNA binding protein (e.g., by a peptide bond). Alternatively, a base editor may include a deaminase and a nucleic acid programmable DNA binding protein that associate noncovalently (e.g., where one or more components of the base editor are supplied in trans and associate directly or via another molecule such as a protein or nucleic acid). In an embodiment, one or more components of the complex are held together by hydrogen bonds.

By “cytosine” or “4-Aminopyrimidin-2(1*H*)-one” is meant a purine nucleobase with



the molecular formula $C_4H_5N_3O$, having the structure to CAS No. 71-30-7.

By “cytidine” is meant a cytosine molecule attached to a ribose sugar via a glycosidic



bond, having the structure , and corresponding to CAS No. 65-46-3.

Its molecular formula is $C_9H_{13}N_3O_5$.

By “Cytidine Base Editor (CBE)” is meant a base editor comprising a cytidine
 5 deaminase. Non-limiting examples of cytidine deaminase base editor amino acid sequences include amino acid sequences for BE4max (SEQ ID NO: 3658), YE1-BE4 (SEQ ID NO: 3659), YE2-BE4 (SEQ ID NO: 3660), YEE-BE4 (SEQ ID NO: 3661), EE-BE4 (SEQ ID NO: 3662), R33A-BE4 (SEQ ID NO: 3663), R33A+K34A-BE4 (SEQ ID NO: 3664), APOBEC3A (A3A)-BE4 (SEQ ID NO: 3665), APOBEC3B (A3B)-BE4 (SEQ ID NO: 3666),
 10 APOBEC3G (A3G)-BE4 (SEQ ID NO: 3667), AID-BE4 (SEQ ID NO: 3668), CDA-BE4 (SEQ ID NO: 3669), FERNY-BE4 (SEQ ID NO: 3670), evolved APOBEC3A (eA3A)-BE4 (SEQ ID NO: 3671), AALN-BE4 (SEQ ID NO: 3672), BE4max modified with SpCas9-NG (SEQ ID NO: 3673), YE1-SpCas9-NG (YE1-NG) (SEQ ID NO: 3674), YE2-SpCas9-NG (SEQ ID NO: 3675), YEE-SpCas9-NG (SEQ ID NO: 3676), EE-SpCas9-NG (SEQ ID NO: 3677), R33A+K34A-SpCas9-NG (SEQ ID NO: 3678), YE1-CP1028 (YE1-BE4-CP1028, or YE1-CP) (SEQ ID NO: 3679), YE2-CP1028 (YE2-BE4-CP1028) (SEQ ID NO: 3680), YEE-CP1028 (YEE-BE4-CP1028) (SEQ ID NO: 3681), EE-CP1028 (EE-BE4-CP1028) (SEQ ID NO: 3682), R33A+K34A-CP1028 (R33A+K34A-BE4-CP1028) (SEQ ID NO: 3683), BE4max (with nickase) (SEQ ID NO: 3702), BE4 (SEQ ID NO: 3703), BE4 with His tag
 20 (SEQ ID NO: 3704), BE4max (SEQ ID NO: 3705), AncBE4max 689 (SEQ ID NO: 3706), and AncBE4max 687 (SEQ ID NO: 3707).

By “Cytidine Base Editor (CBE) polynucleotide” is meant a polynucleotide encoding a CBE. Non-limiting examples of polynucleotide sequences encoding cytidine deaminase base editors include those encoding BE4max (SEQ ID NO: 3721), AncBE4max689 (SEQ ID
 25 NO: 3722), and AncBE4max687 (SEQ ID NO: 3723).

By “cytidine deaminase” or “cytosine deaminase” is meant a polypeptide or fragment thereof capable of deaminating cytidine or cytosine. In embodiments, the cytidine or cytosine is present in a polynucleotide. In one embodiment, the cytidine deaminase converts cytosine

to uracil or 5-methylcytosine to thymine. The terms “cytidine deaminase” and “cytosine deaminase” are used interchangeably throughout the application. *Petromyzon marinus* cytosine deaminase 1 (PmCDA1) (SEQ ID NO: 13-14), Activation-induced cytidine deaminase (AICDA) (SEQ ID NOs: 15-21), and APOBEC (SEQ ID NOs: 12-61) are

5 exemplary cytidine deaminases. Further exemplary cytidine deaminase (CDA) sequences are provided in the Sequence Listing as SEQ ID NOs: 62-66 and SEQ ID NOs: 67-189. Non-limiting examples of cytidine deaminases include those described in PCT/US20/16288, PCT/US2018/021878, 180802-021804/PCT, PCT/US2018/048969, PCT/US2016/058344, PCT/US2020/062428, and PCT/US2019/033848, the disclosures of which are incorporated

10 herein by reference in their entireties for all purposes. Non-limiting examples of cytidine deaminase amino acid sequences include amino acid sequences for Rat APOBEC1 (SEQ ID NO: 3684), Human APOBEC1 (SEQ ID NO: 3685), Human APOBEC3 (SEQ ID NO: 3686), Human APOBEC3B (SEQ ID NO: 3687), Human APOBEC3G (SEQ ID NO: 3688), evoAPOBEC3A(eA3A) (SEQ ID NO: 3689), evoCDA (SEQ ID NO: 3690), evoAPOBEC1

15 (SEQ ID NO: 3691), YE1 (SEQ ID NO: 3692), YE2 (SEQ ID NO: 3693), YEE (SEQ ID NO: 3694), EE (SEQ ID NO: 3695), R33A (SEQ ID NO: 3696), R33A+K34A (SEQ ID NO: 3697), AALN (SEQ ID NO: 3698), FERNY (SEQ ID NO: 3699), evoFERNY (SEQ ID NO: 3700), APOBEC (SEQ ID NO: 3724), Anc686 APOBEC (SEQ ID NO: 3725), Human APOBEC-3G D316R_D317R (SEQ ID NO: 5726), Human APOBEC-3G chain A (SEQ ID

20 NO: 3727), Human APOBEC3-G chain A D120R_D121R (SEQ ID NO: 3728), Mouse APOBEC3 (SEQ ID NO: 3729), Rat APOBEC3 (SEQ ID NO: 3730), Rhesus macaque APOBEC-3G (SEQ ID NO: 3731), Chimpanzee APOBEC-3G (SEQ ID NO: 3732), Green Monkey APOBEC-3G (SEQ ID NO: 3733), Human APOBEC-3G (SEQ ID NO: 3734), Human APOBEC-3F (SEQ ID NO: 3735), Human APOBEC-3B (SEQ ID NO: 3736), Rat

25 APOBEC-3B (SEQ ID NO: 3737), Bovine APOBEC-3B (SEQ ID NO: 3738), Chimpanzee APOBEC-3B (SEQ ID NO: 3739), Gorilla APOBEC-3C (SEQ ID NO: 3740), Human APOBEC-3A (SEQ ID NO: 3741), Rhesus macaque APOBEC-3A (SEQ ID NO: 3742), Bovine APOBEC-3A (SEQ ID NO: 3743), Human APOBEC-3H (SEQ ID NO: 3744), Human APOBEC-3D (SEQ ID NO: 3745), Rat ABOPEC1 (SEQ ID NO: 3746), Anc689

30 APOBEC (SEQ ID NO: 3747), Anc687 APOBEC (SEQ ID NO: 3748), Anc686 APOBEC (SEQ ID NO: 3749), Anc655 APOBEC (SEQ ID NO: 3750), and Anc733 APOBEC (SEQ ID NO: 3751).

By “cytidine deaminase polynucleotide” is meant a polynucleotide encoding a cytidine deaminase. Non-limiting examples of polynucleotide sequences encoding cytidine

deaminase domains include those encoding Rat APOBEC1 (SEQ ID NO: 3709), Anc689 APOBEC (SEQ ID NO: 3710), Anc687 APOBEC (SEQ ID NO: 3711), Anc686 APOBEC (SEQ ID NO: 3712), Anc655 APOBEC (SEQ ID NO: 3713), Anc733 APOBEC (SEQ ID NO: 3714), Rat APOBEC1 (SEQ ID NO: 3715), Anc689 APOBEC (SEQ ID NO: 3716),
5 Anc687 APOBEC (SEQ ID NO: 3717), Anc686 APOBEC (SEQ ID NO: 3718), Anc655 APOBEC (SEQ ID NO: 3719), and Anc733 APOBEC (SEQ ID NO: 3720).

By “cytosine deaminase activity” is meant catalyzing the deamination of cytosine or cytidine. In one embodiment, a polypeptide having cytosine deaminase activity converts an amino group to a carbonyl group. In an embodiment, a cytosine deaminase converts cytosine
10 to uracil (*i.e.*, C to U) or 5-methylcytosine to thymine (*i.e.*, 5mC to T). In some embodiments, a cytosine deaminase as provided herein has increased cytosine deaminase activity (*e.g.*, at least 10-fold, 20-fold, 30-fold, 40-fold, 50-fold, 60-fold, 70-fold, 80-fold, 90-fold, 100-fold or more) relative to a reference cytosine deaminase.

The term “deaminase” or “deaminase domain,” as used herein, refers to a protein or
15 fragment thereof that catalyzes a deamination reaction.

The term “detect” refers to identifying the presence, absence or amount of the analyte to be detected. In one embodiment, a sequence alteration in a polynucleotide or polypeptide is detected. In another embodiment, the presence of indels is detected.

By “detectable label” is meant a composition that when linked to a molecule of
20 interest renders the latter detectable, via spectroscopic, photochemical, biochemical, immunochemical, or chemical means. For example, useful labels include radioactive isotopes, magnetic beads, metallic beads, colloidal particles, fluorescent dyes, electron-dense reagents, enzymes (for example, as commonly used in an enzyme linked immunosorbent assay (ELISA)), biotin, digoxigenin, or haptens.

By “disease” is meant any condition or disorder that damages or interferes with the normal function of a cell, tissue, or organ. Exemplary diseases include diseases amenable to treatment with involving introducing an alteration to a complement complement factor B (CFB) polynucleotide in a cell that results in a reduction in activity and/or expression of a CFB polypeptide in the cell. In some instances, the disease is a disease associated with
30 inappropriate activation of the complement system in the subject. Non-limiting examples of diseases associated with inappropriate activation of the complement system include blood disorders, transplant or graft rejection, inflammatory diseases or disorders, eye diseases or disorders, kidney diseases or disorders, heart disorders, respiratory diseases or disorders, autoimmune disorders, inflammatory bowel diseases or disorders, arthritis, neurodegenerative

diseases or disorders, musculoskeletal diseases or disorders associated with inflammation, disorders affecting the integumentary system, diseases or disorders affecting the central nervous system, diseases or disorders affecting the circulatory system, diseases or disorders affecting the gastrointestinal system, diseases or disorders affecting the thyroid, chronic pain, allergies, and pulmonary diseases. Further non-limiting examples of diseases associated with inappropriate activation of the complement system include paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic syndrome (aHUS), HELLP syndrome, autoimmune hemolytic anemia, transplant rejection, ischemia/reperfusion injury, transplant damage, hyperacute rejection, graft rejection or failure, acute antibody-mediated rejection, chronic inflammation, chronic allograft vasculopathy, chronic rejection of a transplant or graft, age-related macular degeneration (e.g., wet or dry age-related macular degeneration), diabetic retinopathy, glaucoma, uveitis, autoimmune diseases, myasthenia gravis, neuromyelitis optica (NMO), renal disease, membranoproliferative glomerulonephritis (MPGN) (e.g., MPGN type I, type II, or type III), IgA nephropathy (IgAN), primary membranous nephropathy, C3 glomerulopathy, proteinuria, a neurodegenerative disease, neuropathic pain, rhinosinusitis, nasal polyposis, cancer, sepsis, respiratory distress syndrome, anaphylaxis, infusion reaction, a respiratory disease or disorder (e.g., asthma or chronic obstructive pulmonary disease (COPD), oridiopathic pulmonary fibrosis, or asthma), a Th2-associated disorder (e.g., a disorder associated with high levels or high activation of CD4⁺ helper T cells of the Th2 subtype), a disorder associated with high levels or inappropriate activity of CD4⁺ helper T cells of the Th17 subtype, inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis), inflammatory skin diseases, a chronic inflammatory disease, psoriasis, atopic dermatitis, systemic scleroderma, sclerosis, Bechet's disease, dermatomyositis, polymyositis, multiple sclerosis (MS), dermatitis, meningitis, encephalitis, uveitis, osteoarthritis, lupus nephritis, rheumatoid arthritis (RA), Sjoren's syndrome, vasculitis, central nervous system (CNS) inflammatory disorders, chronic hepatitis, chronic pancreatitis, glomerulonephritis, sarcoidosis, thyroiditis, pathologic immune responses to tissue/organ transplantation, bronchiolitis, hypersensitivity pneumonitis, idiopathic pulmonary fibrosis (IPF), periodontitis, gingivitis, a disorder associated with excessive or inappropriate activity of IgE-producing cells, neuromyelitis optica, pemphigoid, pulmonary fibrosis (e.g., idiopathic pulmonary fibrosis), radiation-induced lung injury, allergic bronchopulmonary aspergillosis, hypersensitivity pneumonitis, eosinophilic pneumonia, interstitial pneumonia, sarcoid, Wegener's granulomatosis, bronchiolitis obliterans, allergic rhinitis, an inflammatory joint condition (e.g., arthritis such as rheumatoid

arthritis or psoriatic arthritis, juvenile chronic arthritis, spondyloarthropathies Reiter's syndrome, or gout), a dermatomyositis, polymyositis, chronic muscle inflammation, pemphigus, systemic lupus erythematosus, dermatomyositis, scleroderma, sclerodermatomyositis, Sjögren syndrome, chronic urticaria, a demyelinating disease, amyotrophic lateral sclerosis, chronic pain, stroke, allergic neuritis, Huntington's disease, Alzheimer's disease, Parkinson's disease, a disease of the circulatory system, polyarteritis nodosa, Wegener's granulomatosis, giant cell arteritis, Churg-Strauss syndrome, microscopic polyangiitis, Henoch-Schonlein purpura, Takayasu's arteritis, Kawasaki disease, Behcet's disease, ulcerative colitis, thyroiditis (e.g., Hashimoto's thyroiditis, Graves' disease, post-partum thyroiditis), myocarditis, hepatitis (e.g., hepatitis C), pancreatitis, glomerulonephritis (e.g., membranoproliferative glomerulonephritis or membranous glomerulonephritis), panniculitis, eye disorders, choroidal neovascularization (CNV), retinal neovascularization (RNV), ocular inflammation, retinopathy of prematurity, proliferative vitreoretinopathy, uveitis, keratitis, conjunctivitis, and scleritis, geographic atrophy, conjunctivitis, keratitis, scleritis, iritis, iridocyclitis, cyclitis, pars planitis, choroiditis, persistent asthma, and allergic asthma. In some cases, the disease is selected from glaucoma, diabetic retinopathy, age-related macular degeneration, and neurological diseases such as amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), Alzheimer's disease, and various Tauopathies.

By "dual editing activity" or "dual deaminase activity" is meant having adenosine deaminase and cytidine deaminase activity. In one embodiment, a base editor having dual editing activity has both A→G and C→T activity, wherein the two activities are approximately equal or are within about 10% or 20% of each other. In another embodiment, a dual editor has A→G activity that no more than about 10% or 20% greater than C→T activity. In another embodiment, a dual editor has A→G activity that is no more than about 10% or 20% less than C→T activity. In some embodiments, the adenosine deaminase variant has predominantly cytosine deaminase activity, and little, if any, adenosine deaminase activity. In some embodiments, the adenosine deaminase variant has cytosine deaminase activity, and no significant or no detectable adenosine deaminase activity. Non-limiting examples of proteins having dual deaminase activity include those described in International Patent Application Publications No. WO 2024/040083 and WO 2022/204574, the disclosures of which are hereby incorporated by reference in their entireties for all purposes.

By "effective amount" is meant the amount of an agent (e.g., a base editor, cell) as described herein, that is required to ameliorate the symptoms of a disease relative to an untreated patient or an individual without disease, *i.e.*, a healthy individual, or is the amount

of the agent sufficient to elicit a desired biological response. The effective amount of active compound(s) used to practice embodiments of the present disclosure for therapeutic treatment of a disease varies depending upon the manner of administration, the age, body weight, and general health of the subject. Ultimately, the attending physician or veterinarian will decide the appropriate amount and dosage regimen. Such amount is referred to as an “effective” amount. In one embodiment, an effective amount is the amount of a base editor of the disclosure sufficient to introduce an alteration in a gene of interest in a cell (*e.g.*, a cell *in vitro* or *in vivo*). In one embodiment, an effective amount is the amount of a base editor required to achieve a therapeutic effect. Such therapeutic effect need not be sufficient to alter a pathogenic gene in all cells of a subject, tissue or organ, but only to alter the pathogenic gene in about 1%, 5%, 10%, 25%, 50%, 75% or more of the cells present in a subject, tissue or organ. In one embodiment, an effective amount is sufficient to ameliorate one or more symptoms of a disease.

By “fragment” is meant a portion of a polypeptide or nucleic acid molecule. This portion contains, at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% of the entire length of the reference nucleic acid molecule or polypeptide. A fragment may contain 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100, 200, 300, 400, 500, 600, 700, 800, 900, or 1000 nucleotides or amino acids. In some embodiments, the fragment is a functional fragment.

By “guide polynucleotide” is meant a polynucleotide or polynucleotide complex which is specific for a target sequence and can form a complex with a polynucleotide programmable nucleotide binding domain protein (*e.g.*, Cas9 or Cpf1). In an embodiment, the guide polynucleotide is a guide RNA (gRNA). gRNAs can exist as a complex of two or more RNAs, or as a single RNA molecule.

“Hybridization” means hydrogen bonding, which may be Watson-Crick, Hoogsteen or reversed Hoogsteen hydrogen bonding, between complementary nucleobases. For example, adenine and thymine are complementary nucleobases that pair through the formation of hydrogen bonds.

By “inappropriate activation” in the context of factor B is meant any increase in complement activation that is associated with a disease or disorder. In an embodiment, inappropriate activation is activation that is increased or elevated locally (*e.g.*, in an organ or tissue, such as in the central nervous system or in an eye) or systemically relative to a healthy reference (*e.g.*, a healthy subject). In some instances “inappropriate activation” is activation that is associated with chronic (*e.g.*, lasting more than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 weeks) inflammation in a subject. In some cases, inappropriate activation is

activation that is directed against a tissue, cell, or organ of a subject and/or that leads to undesired damage to the tissue, cell, or organ of the subject. In embodiments, a disease or disorder associated with inappropriate activation of the complement system can be treated by any of the methods or compositions provided herein for reducing or eliminating expression and/or activity of a factor B polypeptide. In an embodiment, complement activation is detected by measuring levels of a factor B polypeptide and/or of a cleaved factor B polypeptide (e.g., a Ba fragment or a Bb fragment), where inappropriate activation can be determined as high levels of the factor B polypeptide and/or cleaved factor B polypeptide relative to a healthy reference subject.

By “increases” is meant a positive alteration of at least 10%, 25%, 50%, 75%, or 100%, or about 1.5 fold, about 2 fold, about 3-fold, about 4-fold, about 5-fold, about 6-fold, about 7-fold, about 8-fold, about 9-fold, about 10-fold, about 15-fold, about 20-fold, about 25-fold, about 30-fold, about 35-fold, about 40-fold, about 45-fold, about 50-fold, or about 100-fold.

The terms “inhibitor of base repair”, “base repair inhibitor”, “IBR” or their grammatical equivalents refer to a protein that is capable in inhibiting the activity of a nucleic acid repair enzyme, for example a base excision repair enzyme.

An “intein” is a fragment of a protein that is able to excise itself and join the remaining fragments (the exteins) with a peptide bond in a process known as protein splicing. The process of an intein excising itself and joining the remaining portions of the protein is herein termed “protein splicing” or “intein-mediated protein splicing.” In some embodiments, an intein is a trans-splicing intein (also referred to as a “split intein”). In the case of trans-splicing inteins, a full-length polypeptide is split into two separate fragments and the C-terminus of the N-terminal fragment is fused to an N-terminal fragment of a split intein (N-intein) and the N-terminus of the remaining C-terminal fragment is fused to a C-terminal fragment of a split intein (C-intein). Not intending to be bound by theory or mechanism of action, contacting the two polypeptide sequences with one another results in excision of the intein and joining of the two polypeptide sequences together to form a full-length polypeptide sequence. In embodiments, contacting the two polypeptide fragments each fused to an intein fragment, or peptide derived from an intein fragment, is associated with a measured catalytic activity (e.g., deamination of a nucleobase in a polynucleotide sequence) in a cell that is greater than that observed when the two polypeptide fragments are contacted with one another in a cell and do not contain any intein fragments. Non-limiting examples of N-intein

and C-intein sequences include those sequences sharing at least 85% sequence identity to an amino acid sequence listed in **Table A** or **Table B**, or functional fragments thereof.

Table A. Representative synthetic N-intein amino acid sequences.

Intein	Sequence	SEQ ID NO
Syn2-N	CLSYDTEILTVEYGLIPIGEIVEKKIECTVYTIDNNGLI YTQSIEQWHHRGYQELFEYILEDGSTIRATKDHKFMFTSE RQMLPIEEIFERGWELKQVL	3560
Syn3-N	CLSSDTEVITEEYGPIAIGKIVDEGIRCSVYSVDNNGNL YTQPISQWHDGRGRQEIYEYYLENGSVIRATKDHKFMFTKD GEMPLIDEIFEKGLELQVLP	3561
Syn5-N	CLSYETEVLTVYEGFMPIGKIVEERIRCSVYTVDKNGFI YSQPIAQWHQRGLQEVYDYDLENGSIIRATKEHQFMTND GQMLAIHEIFTRKLDLLQSQE	3562

Table B. Representative synthetic C-intein amino acid sequences.

Intein	Sequence	SEQ ID NO
Syn1-C	MKVISRKSLGTQPVYDICTVTHDHNFLMKNGLIASN	3563
Syn4-C	MDVKIVSYKFLGSENVYDILERDHNFLIKNGLVASN	3564
Syn5-C	MVKIITYKSLGRQKVYDLGLEQDHNFVLANGLVASN	3565
Syn9-C	MVKIISRKYLDTPVYDVGVQKDHNFLLISNGSIASN	3566
Syn10-C	MVKIATRRSLGTEPVYDIGLQQEHNFLLANGLVASN	3567

The terms “isolated,” “purified,” or “biologically pure” refer to material that is free to varying degrees from components which normally accompany it as found in its native state.

“Isolate” denotes a degree of separation from original source or surroundings. “Purify” denotes a degree of separation that is higher than isolation. A “purified” or “biologically pure” protein is sufficiently free of other materials such that any impurities do not materially affect the biological properties of the protein or cause other adverse consequences. That is, a nucleic acid or peptide of this disclosure is purified if it is substantially free of cellular material, viral material, or culture medium when produced by recombinant DNA techniques, or chemical precursors or other chemicals when chemically synthesized. Purity and homogeneity are typically determined using analytical chemistry techniques, for example, polyacrylamide gel electrophoresis or high performance liquid chromatography. The term “purified” can denote that a nucleic acid or protein gives rise to essentially one band in an electrophoretic gel. For a protein that can be subjected to modifications, for example,

phosphorylation or glycosylation, different modifications may give rise to different isolated proteins, which can be separately purified.

By “isolated polynucleotide” is meant a nucleic acid molecule that is free of the genes which, in the naturally-occurring genome of the organism from which the nucleic acid molecule of the disclosure is derived, flank the gene. The term therefore includes, for example, a recombinant DNA that is incorporated into a vector; into an autonomously replicating plasmid or virus; or into the genomic DNA of a prokaryote or eukaryote; or that exists as a separate molecule (for example, a cDNA or a genomic or cDNA fragment produced by PCR or restriction endonuclease digestion) independent of other sequences. In addition, the term includes an RNA molecule that is transcribed from a DNA molecule, as well as a recombinant DNA that is part of a hybrid gene encoding additional polypeptide sequence.

By an “isolated polypeptide” is meant a polypeptide of the disclosure that has been separated from components that naturally accompany it. Typically, the polypeptide is isolated when it is at least 60%, by weight, free from the proteins and naturally-occurring organic molecules with which it is naturally associated. In embodiments, the preparation is at least 75%, at least 90%, or at least 99%, by weight, a polypeptide of the disclosure. An isolated polypeptide of the disclosure may be obtained, for example, by extraction from a natural source, by expression of a recombinant nucleic acid encoding such a polypeptide; or by chemically synthesizing the protein. Purity can be measured by any appropriate method, for example, column chromatography, polyacrylamide gel electrophoresis, or by HPLC analysis.

The term “linker”, as used herein, refers to a molecule that links two moieties. In one embodiment, the term “linker” refers to a covalent linker (*e.g.*, covalent bond) or a non-covalent linker.

By “marker” is meant any protein or polynucleotide having an alteration in expression, level, structure, or activity that is associated with a disease or disorder. In embodiments, the disease or disorder is associated with inappropriate activation of the complement system. In some cases, the marker is a factor B polynucleotide or polypeptide.

The term “mutation,” as used herein, refers to a substitution of a residue within a sequence, *e.g.*, a nucleic acid or amino acid sequence, with another residue, or a deletion or insertion of one or more residues within a sequence. Mutations are typically described herein by identifying the original residue followed by the position of the residue within the sequence and by the identity of the newly substituted residue. Various methods for making the amino acid substitutions (mutations) provided herein are well known in the art, and are provided by,

for example, Green and Sambrook, *Molecular Cloning: A Laboratory Manual* (4th ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (2012)).

The terms “nucleic acid” and “nucleic acid molecule,” as used herein, refer to a compound comprising a nucleobase and an acidic moiety, *e.g.*, a nucleoside, a nucleotide, or
5 a polymer of nucleotides. Typically, polymeric nucleic acids, *e.g.*, nucleic acid molecules comprising three or more nucleotides are linear molecules, in which adjacent nucleotides are linked to each other via a phosphodiester linkage. In some embodiments, “nucleic acid” refers to individual nucleic acid residues (*e.g.*, nucleotides and/or nucleosides). In some
10 embodiments, “nucleic acid” refers to an oligonucleotide chain comprising three or more individual nucleotide residues. As used herein, the terms “oligonucleotide” and “polynucleotide” can be used interchangeably to refer to a polymer of nucleotides (*e.g.*, a string of at least three nucleotides). In some embodiments, “nucleic acid” encompasses RNA as well as single and/or double-stranded DNA. Nucleic acids may be naturally occurring, for
15 example, in the context of a genome, a transcript, an mRNA, tRNA, rRNA, siRNA, snRNA, a plasmid, cosmid, chromosome, chromatid, or other naturally occurring nucleic acid molecule. On the other hand, a nucleic acid molecule may be a non-naturally occurring molecule, *e.g.*, a recombinant DNA or RNA, an artificial chromosome, an engineered genome, or fragment thereof, or a synthetic DNA, RNA, DNA/RNA hybrid, or including
20 non-naturally occurring nucleotides or nucleosides. Furthermore, the terms “nucleic acid,” “DNA,” “RNA,” and/or similar terms include nucleic acid analogs, *e.g.*, analogs having other than a phosphodiester backbone. Nucleic acids can be purified from natural sources, produced using recombinant expression systems and optionally purified, chemically synthesized, *etc.* Where appropriate, *e.g.*, in the case of chemically synthesized molecules, nucleic acids comprise nucleoside analogs such as analogs having chemically modified bases
25 or sugars, and backbone modifications. A nucleic acid sequence is presented in the 5' to 3' direction unless otherwise indicated. In some embodiments, a nucleic acid is or comprises natural nucleosides (*e.g.* adenosine, thymidine, guanosine, cytidine, uridine, deoxyadenosine, deoxythymidine, deoxyguanosine, and deoxycytidine); nucleoside analogs (*e.g.*, 2-aminoadenosine, 2-thiothymidine, inosine, pyrrolo-pyrimidine, 3-methyl adenosine, 5-methylcytidine, 2-aminoadenosine, C5-bromouridine, C5-fluorouridine, C5-iodouridine, C5-propynyl-uridine, C5-propynyl-cytidine, C5-methylcytidine, 2-aminoadenosine, 7-deazaadenosine, 7-deazaguanosine, 8-oxoadenosine, 8-oxoguanosine, O(6)-methylguanine, and 2-thiocytidine); chemically modified bases; biologically modified bases (*e.g.*, methylated
30 bases); intercalated bases; modified sugars (*e.g.*, 2'-fluororibose, ribose, 2'-deoxyribose,

arabinose, and hexose); and/or modified phosphate groups (*e.g.*, phosphorothioates and 5'-*N*-phosphoramidite linkages).

The term “nuclear localization sequence,” “nuclear localization signal,” or “NLS” refers to an amino acid sequence that promotes import of a protein into the cell nucleus.

- 5 Nuclear localization sequences are known in the art and described, for example, in Plank *et al.*, International PCT application, PCT/EP2000/011690, filed November 23, 2000, published as WO/2001/038547 on May 31, 2001, the contents of which are incorporated herein by reference for their disclosure of exemplary nuclear localization sequences. In other
- embodiments, the NLS is an optimized NLS described, for example, by Koblan *et al.*, Nature
- 10 Biotech. 2018 doi:10.1038/nbt.4172. In some embodiments, an NLS comprises the amino acid sequence KRTADGSEFESPKKKRKV (SEQ ID NO: 190), KRPAATKKAGQAKKKK (SEQ ID NO: 191), KKTELQTTNAENKTKKL (SEQ ID NO: 192), KRGINDRNFWRGENGRKTR (SEQ ID NO: 193), RKSGKIAAIVVKRPRK (SEQ ID NO: 194), PKKKRKV (SEQ ID NO: 195), MDSLMLNRRKFLYQFKNVRWAKGRRETYLC (SEQ ID NO: 196),
- 15 PKKKRKVEGADKRTADGSEFESPKKKRKV (SEQ ID NO: 328), or RKSGKIAAIVVKRPRKPKKKRKV (SEQ ID NO: 329).

- The term “nucleobase,” “nitrogenous base,” or “base,” used interchangeably herein, refers to a nitrogen-containing biological compound that forms a nucleoside, which in turn is a component of a nucleotide. The ability of nucleobases to form base pairs and to stack one
- 20 upon another leads directly to long-chain helical structures such as ribonucleic acid (RNA) and deoxyribonucleic acid (DNA). Five nucleobases – adenine (A), cytosine (C), guanine (G), thymine (T), and uracil (U) – are called primary or canonical. Adenine and guanine are derived from purine, and cytosine, uracil, and thymine are derived from pyrimidine. DNA and RNA can also contain other (non-primary) bases that are modified. Non-limiting
- 25 exemplary modified nucleobases can include hypoxanthine, xanthine, 7-methylguanine, 5,6-dihydrouracil, 5-methylcytosine (m5C), and 5-hydromethylcytosine. Hypoxanthine and xanthine can be created through mutagen presence, both of them through deamination (replacement of the amine group with a carbonyl group). Hypoxanthine can be modified from adenine. Xanthine can be modified from guanine. Uracil can result from deamination of
- 30 cytosine. A “nucleoside” consists of a nucleobase and a five carbon sugar (either ribose or deoxyribose). Examples of a nucleoside include adenosine, guanosine, uridine, cytidine, 5-methyluridine (m5U), deoxyadenosine, deoxyguanosine, thymidine, deoxyuridine, and deoxycytidine. Examples of a nucleoside with a modified nucleobase includes inosine (I),

xanthosine (X), 7-methylguanosine (m7G), dihydrouridine (D), 5-methylcytidine (m5C), and pseudouridine (Ψ). A “nucleotide” consists of a nucleobase, a five carbon sugar (either ribose or deoxyribose), and at least one phosphate group. Non-limiting examples of modified nucleobases and/or chemical modifications that a modified nucleobase may include are the following: pseudo-uridine, 5-Methyl-cytosine, 2'-*O*-methyl-3'-phosphonoacetate, 2'-*O*-methyl thioPACE (MSP), 2'-*O*-methyl-PACE (MP), 2'-fluoro RNA (2'-F-RNA), constrained ethyl (S-cEt), 2'-*O*-methyl ('M'), 2'-*O*-methyl-3'-phosphorothioate ('MS'), 2'-*O*-methyl-3'-thiophosphonoacetate ('MSP'), 5-methoxyuridine, phosphorothioate, and N1-Methylpseudouridine.

10 The term “nucleic acid programmable DNA binding protein” or “napDNAbp” may be used interchangeably with “polynucleotide programmable nucleotide binding domain” to refer to a protein that associates with a nucleic acid (*e.g.*, DNA or RNA), such as a guide nucleic acid or guide polynucleotide (*e.g.*, gRNA), that guides the napDNAbp to a specific nucleic acid sequence. In some embodiments, the polynucleotide programmable nucleotide binding domain is a polynucleotide programmable DNA binding domain. In some
15 embodiments, the polynucleotide programmable nucleotide binding domain is a polynucleotide programmable RNA binding domain. In some embodiments, the polynucleotide programmable nucleotide binding domain is a Cas9 protein. A Cas9 protein can associate with a guide RNA that guides the Cas9 protein to a specific DNA sequence that
20 is complementary to the guide RNA. In some embodiments, the napDNAbp is a Cas9 domain, for example a nuclease active Cas9, a Cas9 nickase (nCAs9), or a nuclease inactive Cas9 (dCas9). Non-limiting examples of nucleic acid programmable DNA binding proteins include, Cas9 (*e.g.*, dCas9 and nCas9), Cas12a/Cpf1, Cas12b/C2cl, Cas12c/C2c3, Cas12d/CasY, Cas12e/CasX, Cas12g, Cas12h, Cas12i, and Cas12j/CasΦ (Cas12j/Casphi).
25 Non-limiting examples of Cas enzymes include Cas1, Cas1B, Cas2, Cas3, Cas4, Cas5, Cas5d, Cas5t, Cas5h, Cas5a, Cas6, Cas7, Cas8, Cas8a, Cas8b, Cas8c, Cas9 (also known as Csn1 or Csx12), Cas10, Cas10d, Cas12a/Cpf1, Cas12b/C2cl, Cas12c/C2c3, Cas12d/CasY, Cas12e/CasX, Cas12g, Cas12h, Cas12i, Cas12j/CasΦ, Cpf1, Csy1, Csy2, Csy3, Csy4, Cse1, Cse2, Cse3, Cse4, Cse5e, Csc1, Csc2, Csa5, Csn1, Csn2, Csm1, Csm2, Csm3, Csm4, Csm5,
30 Csm6, Cmr1, Cmr3, Cmr4, Cmr5, Cmr6, Csb1, Csb2, Csb3, Csx17, Csx14, Csx10, Csx16, CsaX, Csx3, Csx1, Csx1S, Csx11, Csf1, Csf2, CsO, Csf4, Csd1, Csd2, Cst1, Cst2, Csh1, Csh2, Csa1, Csa2, Csa3, Csa4, Csa5, Type II Cas effector proteins, Type V Cas effector proteins, Type VI Cas effector proteins, CARF, DinG, homologues thereof, or modified or engineered versions thereof. Other nucleic acid programmable DNA binding proteins are also

within the scope of this disclosure, although they may not be specifically listed in this disclosure. See, e.g., Makarova *et al.* “Classification and Nomenclature of CRISPR-Cas Systems: Where from Here?” *CRISPR J.* 2018 Oct;1:325-336. doi: 10.1089/crispr.2018.0033; Yan *et al.*, “Functionally diverse type V CRISPR-Cas systems” *Science*. 2019 Jan 4;363(6422):88-91. doi: 10.1126/science.aav7271, the entire contents of each are hereby incorporated by reference. Exemplary nucleic acid programmable DNA binding proteins and nucleic acid sequences encoding nucleic acid programmable DNA binding proteins are provided in the Sequence Listing as SEQ ID NOs: 197-231, 232-245, 254-257, 260, and 378. In some embodiments, the napDNAbp is a (CRISPR-associated system) Cas9 endonuclease, for example, Cas9 (CsnI) from *Streptococcus pyogenes* (e.g., SEQ ID NO: 197), Cas9 from *Neisseria meningitidis* (NmeCas9; SEQ ID NO: 208), Nme2Cas9 (SEQ ID NO: 209), *Streptococcus constellatus* (ScoCas9), or derivatives thereof (e.g., a sequence with at least about 85% sequence identity to a Cas9, such as Nme2Cas9 or spCas9). Further non-limiting examples of nucleic acid programmable DNA binding proteins include those disclosed or referenced in Rufflow, *et al.*, “Design of highly functional genome editors by modeling of the universe of CRISPR-Cas Sequences,” *bioRxiv*, posted April 22, 2024, doi: 10.1101/2024.04.22.590591, the disclosure of which is incorporated herein by reference in its entirety for all purposes, which were designed using artificial intelligence. In some embodiments, the napDNAbp is OpenCRISPR-1, or a variant thereof (e.g., a variant comprising a D10A amino acid alteration and/or lacking an N-terminal methionine). Further non-limiting examples of nucleic acid programmable DNA binding proteins include those disclosed in International Patent Application No. PCT/US2019/047996.

The terms “nucleobase editing domain” or “nucleobase editing protein,” as used herein, refers to a protein or enzyme that can catalyze a nucleobase modification in RNA or DNA, such as cytosine (or cytidine) to uracil (or uridine) or thymine (or thymidine), and adenine (or adenosine) to hypoxanthine (or inosine) deaminations, as well as non-templated nucleotide additions and insertions. In some embodiments, the nucleobase editing domain is a deaminase domain (e.g., an adenine deaminase or an adenosine deaminase; or a cytidine deaminase or a cytosine deaminase).

As used herein, “obtaining” as in “obtaining an agent” includes synthesizing, purchasing, or otherwise acquiring the agent.

By “OpenCRISPR-1 polypeptide” is meant a protein with an amino acid sequence having at least about 85% amino acid sequence identity to SEQ ID NO: 3568, or a fragment thereof that associates with a nucleic acid, such as a guide nucleic acid or guide

polynucleotide, that guides the napDNAbp to a specific nucleic acid sequence. Further details relating to the OpenCRISPR-1 polypeptide are disclosed in Rufflow, *et al.*, “Design of highly functional genome editors by modeling of the universe of CRISPR-Cas Sequences,” *bioRxiv*, posted April 22, 2024, doi: 10.1101/2024.04.22.590591, the disclosure of which is
 5 incorporated herein by reference in its entirety for all purposes.

By “OpenCRISPR-1 polynucleotide” is meant a nucleic acid molecule encoding an OpenCRISPR-1 polypeptide, as well as the introns, exons, 3' untranslated regions, 5' untranslated regions, and regulatory sequences associated with its expression, or fragments thereof. In embodiments, an OpenCRISPR-1 polynucleotide is the genomic sequence, cDNA,
 10 mRNA, or gene associated with and/or required for OpenCRISPR-1 expression. An exemplary OpenCRISPR-1 nucleotide sequence is provided at SEQ ID NO: 3569.

In various embodiments, a guide RNA suitable for use in combination with an OpenCRISPR-1 polypeptide contains a scaffold having at least 85% sequence identity to a nucleotide sequence selected from the following, or fragments thereof capable of binding to
 15 an OpenCRISPR-1 polypeptide:

GUUUUAGAGCUGUGUUGAAAAACACAGCAAGUUAUUAAAGGCUUUGUCCGUAUCCAACUUG
 AAAAAGUGAGCACCGAUUCGGUGC (SEQ ID NO: 3570);
 GUUUUAGAGCUGGAAACAGCAAGUUAUUAAAGGCUUUGUCCGUAUCCAACUUGAAAAAGUG
 AGCACCGAUUCGGUGC (SEQ ID NO: 3571); and
 20 GUUUUAGAGCUAGAAUAGCAAGUUAUUAAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGG
 CACCGAGUCGGUGC (SEQ ID NO: 3572).

By “subject” or “patient” is meant a mammal, including, but not limited to, a human or non-human mammal. In embodiments, the mammal is a bovine, equine, canine, ovine, rabbit, rodent, nonhuman primate, or feline. In an embodiment, “patient” refers to a
 25 mammalian subject with a higher than average likelihood of developing a disease or a disorder. Exemplary patients can be humans, non-human primates, cats, dogs, pigs, cattle, cats, horses, camels, llamas, goats, sheep, rodents (*e.g.*, mice, rabbits, rats, or guinea pigs) and other mammals that can benefit from the therapies disclosed herein. Exemplary human patients can be male and/or female.

30 “Patient in need thereof” or “subject in need thereof” is referred to herein as a patient diagnosed with, at risk or having, predetermined to have, or suspected of having a disease or disorder.

The terms “pathogenic mutation”, “pathogenic variant”, “disease causing mutation”, “disease causing variant”, “deleterious mutation”, or “predisposing mutation” refers to a genetic alteration or mutation that is associated with a disease or disorder or that increases an individual’s susceptibility or predisposition to a certain disease or disorder. In some
5 embodiments, the pathogenic mutation comprises at least one wild-type amino acid substituted by at least one pathogenic amino acid in a protein encoded by a gene.

The terms “protein”, “peptide”, “polypeptide”, and their grammatical equivalents are used interchangeably herein, and refer to a polymer of amino acid residues linked together by peptide (amide) bonds. A protein, peptide, or polypeptide can be naturally occurring,
10 recombinant, or synthetic, or any combination thereof.

The term “fusion protein” as used herein refers to a hybrid polypeptide which comprises protein domains from at least two different proteins.

The term “recombinant” as used herein in the context of proteins or nucleic acids refers to proteins or nucleic acids that do not occur in nature but are the product of human
15 engineering. For example, in some embodiments, a recombinant protein or nucleic acid molecule comprises an amino acid or nucleotide sequence that comprises at least one, at least two, at least three, at least four, at least five, at least six, or at least seven mutations as compared to any naturally occurring sequence.

By “reduces” is meant a negative alteration of at least 10%, 25%, 50%, 75%, or
20 100%.

By “reference” is meant a standard or control condition. In one embodiment, the reference is a wild-type or healthy cell. In other embodiments and without limitation, a reference is an untreated cell that is not subjected to a test condition, or is subjected to placebo or normal saline, medium, buffer, and/or a control vector that does not harbor a
25 polynucleotide of interest. In embodiments, a reference is a healthy subject or cell without inappropriate activation of the complement system. In some cases, a reference is an unedited or untreated cell (e.g., a hepatocyte), tissue (e.g., component of the central nervous system or an organ, such as a liver, eye) and/or subject. In embodiments, a reference is a subject not administered a composition of the disclosure or a component thereof. In some cases, a
30 reference is a subject prior to a change in treatment.

A “reference sequence” is a defined sequence used as a basis for sequence comparison. A reference sequence may be a subset of or the entirety of a specified sequence; for example, a segment of a full-length cDNA or gene sequence, or the complete cDNA or gene sequence. For polypeptides, the length of the reference polypeptide sequence will

generally be at least about 16 amino acids, at least about 20 amino acids, at least about 25 amino acids, about 35 amino acids, about 50 amino acids, or about 100 amino acids. For nucleic acids, the length of the reference nucleic acid sequence will generally be at least about 50 nucleotides, at least about 60 nucleotides, at least about 75 nucleotides, about 100
5 nucleotides or about 300 nucleotides or any integer thereabout or therebetween. In some embodiments, a reference sequence is a wild-type sequence of a protein of interest. In other embodiments, a reference sequence is a polynucleotide sequence encoding a wild-type protein.

The term “RNA-programmable nuclease,” and “RNA-guided nuclease” refer to a
10 nuclease that forms a complex with (*e.g.*, binds or associates with) one or more RNA(s) that is not a target for cleavage. In some embodiments, an RNA-programmable nuclease, when in a complex with an RNA, may be referred to as a nuclease-RNA complex. Typically, the bound RNA(s) is referred to as a guide RNA (gRNA). In some embodiments, the RNA-programmable nuclease is the (CRISPR-associated system) Cas9 endonuclease, for example,
15 Cas9 (CsnI) from *Streptococcus pyogenes* (*e.g.*, SEQ ID NO: 197), Cas9 from *Neisseria meningitidis* (NmeCas9; SEQ ID NO: 208), Nme2Cas9 (SEQ ID NO: 209), *Streptococcus constellatus* (ScoCas9), or derivatives thereof (*e.g.*, a sequence with at least about 85% sequence identity to a Cas9, such as Nme2Cas9 or spCas9).

By “specifically binds” is meant a nucleic acid molecule, polypeptide,
20 polypeptide/polynucleotide complex, compound, or molecule that recognizes and binds a polypeptide and/or nucleic acid molecule of the disclosure, but which does not substantially recognize and bind other molecules in a sample, for example, a biological sample.

By “substantially identical” is meant a polypeptide or nucleic acid molecule exhibiting at least 50% identity to a reference amino acid sequence. In one embodiment, a
25 reference sequence is a wild-type amino acid or nucleic acid sequence. In another embodiment, a reference sequence is any one of the amino acid or nucleic acid sequences described herein. In one embodiment, such a sequence is at least about 60%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.9%, or even 99.99%, identical at the amino acid level or nucleic acid level to the sequence used for comparison.

30 Sequence identity is typically measured using sequence analysis software (for example, Sequence Analysis Software Package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 1710 University Avenue, Madison, Wis. 53705, BLAST, BESTFIT, GAP, or PILEUP/PRETTYBOX programs). Such software matches identical or similar sequences by assigning degrees of homology to various substitutions,

deletions, and/or other modifications. Conservative substitutions typically include substitutions within the following groups: glycine, alanine; valine, isoleucine, leucine; aspartic acid, glutamic acid, asparagine, glutamine; serine, threonine; lysine, arginine; and phenylalanine, tyrosine.

5 Nucleic acid molecules useful in the methods of the disclosure include any nucleic acid molecule that encodes a polypeptide of the disclosure or a functional fragment thereof. Such nucleic acid molecules need not be 100% identical with an endogenous nucleic acid sequence but will typically exhibit substantial identity. Polynucleotides having “substantial identity” to an endogenous sequence are typically capable of hybridizing with at least one
10 strand of a double-stranded nucleic acid molecule. Nucleic acid molecules useful in the methods of the disclosure include any nucleic acid molecule that encodes a polypeptide of the disclosure or a functional fragment thereof. Such nucleic acid molecules need not be 100% identical with an endogenous nucleic acid sequence but will typically exhibit substantial identity. Polynucleotides having “substantial identity” to an endogenous sequence are
15 typically capable of hybridizing with at least one strand of a double-stranded nucleic acid molecule. By “hybridize” is meant pair to form a double-stranded molecule between complementary polynucleotide sequences (*e.g.*, a gene described herein), or portions thereof, under various conditions of stringency. (See, *e.g.*, Wahl, G. M. and S. L. Berger (1987) *Methods Enzymol.* 152:399; Kimmel, A. R. (1987) *Methods Enzymol.* 152:507).

20 By “split” is meant divided into two or more fragments.

A “split polypeptide” or “split protein” refers to a protein that is provided as an N-terminal fragment and a C-terminal fragment translated as two separate polypeptides from a nucleotide sequence(s). The polypeptides corresponding to the N-terminal portion and the C-terminal portion of the split protein may be spliced in some embodiments to form a
25 “reconstituted” protein. In embodiments, the split polypeptide is a nucleic acid programmable DNA binding protein (*e.g.* a Cas9) or a base editor.

The term “target site” refers to a nucleotide sequence or nucleobase of interest within a nucleic acid molecule that is modified. In embodiments, the modification is deamination of a base. The deaminase can be a cytidine or an adenine deaminase. The fusion protein or base
30 editing complex comprising a deaminase may comprise a dCas9-adenosine deaminase fusion protein, a Cas12b-adenosine deaminase fusion, or a base editor disclosed herein.

As used herein, the terms “treat,” “treating,” “treatment,” and the like refer to reducing or ameliorating a disorder and/or symptoms associated therewith or obtaining a desired pharmacologic and/or physiologic effect. It will be appreciated that, although not precluded,

treating a disorder or condition does not require that the disorder, condition or symptoms associated therewith be completely eliminated. In some embodiments, the effect is therapeutic, *i.e.*, without limitation, the effect partially or completely reduces, diminishes, abrogates, abates, alleviates, reduces the intensity of, or cures a disease and/or adverse symptom attributable to the disease. In some embodiments, the effect is preventative, *i.e.*, the effect protects or prevents an occurrence or reoccurrence of a disease or condition. To this end, the presently disclosed methods comprise administering a therapeutically effective amount of a composition as described herein.

By "uracil glycosylase inhibitor" or "UGI" is meant an agent that inhibits the uracil-excision repair system. Base editors comprising a cytidine deaminase convert cytosine to uracil, which is then converted to thymine through DNA replication or repair. In various embodiments, a uracil DNA glycosylase (UGI) prevent base excision repair which changes the U back to a C. In some instances, contacting a cell and/or polynucleotide with a UGI and a base editor prevents base excision repair which changes the U back to a C. An exemplary UGI comprises an amino acid sequence as follows:

>splP14739IUNGI_BPPB2 Uracil-DNA glycosylase inhibitor
MTNLSDIIEKETGKQLVIQESILMLPEEVEEVIGNKPESDILVHTAYDESTDENVMLLTSDA
PEYKPPWALVIQDSNGENKIKML (SEQ ID NO: 231).

In some embodiments, the agent inhibiting the uracil-excision repair system is a uracil stabilizing protein (USP). See, e.g., WO 2022015969 A1, incorporated herein by reference.

As used herein, the term "vector" refers to a means of introducing a nucleic acid molecule into a cell, resulting in a transformed cell. Vectors include plasmids, transposons, phages, viruses, liposomes, lipid nanoparticles, and episomes.

Ranges provided herein are understood to be shorthand for all of the values within the range. For example, a range of 1 to 50 is understood to include any number, combination of numbers, or sub-range from the group consisting 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50.

The recitation of a listing of chemical groups in any definition of a variable herein includes definitions of that variable as any single group or combination of listed groups. The recitation of an embodiment for a variable or aspect herein includes that embodiment as any single embodiment or in combination with any other embodiments or portions thereof.

All terms are intended to be understood as they would be understood by a person skilled in the art. Unless defined otherwise, all technical and scientific terms used herein have

the same meaning as commonly understood by one of ordinary skill in the art to which the disclosure pertains

In this application, the use of the singular includes the plural unless specifically stated otherwise. It must be noted that, as used in the specification, the singular forms “a,” “an” and “the” include plural referents unless the context clearly dictates otherwise. In this application, the use of “or” means “and/or” unless stated otherwise. Furthermore, use of the term “including” as well as other forms, such as “include,” “includes,” and “included,” is not limiting.

As used in this specification and claim(s), the words “comprising” (and any form of comprising, such as “comprise” and “comprises”), “having” (and any form of having, such as “have” and “has”), “including” (and any form of including, such as “includes” and “include”) or “containing” (and any form of containing, such as “contains” and “contain”) are inclusive or open-ended. This wording indicates that specified elements, features, components, and/or method steps are present, but does not exclude the presence of other elements, features, components, and/or method steps. Any embodiments specified as “comprising” a particular component(s) or element(s) are also contemplated as “consisting of” or “consisting essentially of” the particular component(s) or element(s) in some embodiments. It is contemplated that any embodiment discussed in this specification can be implemented with respect to any method or composition of the present disclosure, and vice versa. Furthermore, compositions of the present disclosure can be used to achieve methods of the present disclosure.

The term “about” or “approximately” means within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, *i.e.*, the limitations of the measurement system.

Reference in the specification to “some embodiments,” “an embodiment,” “one embodiment” or “other embodiments” means that a particular feature, structure, or characteristic described in connection with the embodiments is included in at least some embodiments, but not necessarily all embodiments, of the present disclosures.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 provides a schematic diagram depicting the alternative pathway of complement amplification.

FIG. 2 provides a bar graph showing maximum percent A to G base editing of a factor B polynucleotide measured in HEK293T cells transfected with base editor systems

containing an adenosine deaminase and the guides indicated along the x-axis. A base editor system containing the guide sg23 and an adenosine deaminase was used as a positive control for base editing.

FIG. 3 provides a bar graph showing maximum percent C to T base editing of a factor B polynucleotide measured in HEK293T cells transfected with base editor systems containing a cytidine deaminase and the guides indicated along the x-axis. A base editor system containing the guide sg23 and a cytidine deaminase was used as a positive control for base editing.

FIG. 4 provides a bar graph showing maximum percent A to G base editing of a factor B polynucleotide measured in HEK293T cells transfected with base editor systems containing the indicated adenosine deaminases and guide polynucleotides. In **FIG. 4**, the term “NHP X-Reactivity” means “non-human primate cross-reactivity.” A base editor system with NHP X-Reactivity will edit both a human a non-human primate factor B polynucleotide. Each set of bars, from left-to-right, correspond to base editor systems containing the following guide polynucleotides, respectively: gRNA1193, gRNA1120, gRNA1230, gRNA1217, gRNA1204, gRNA1218, gRNA1203, gRNA1202, gRNA1190, gRNA1213, gRNA1210, and sg23. The guide polynucleotide sg23 was used as a positive control.

FIG. 5 provides a bar graph showing human complement factor B (hCFB) protein levels (left axis and left bar of each pair of bars) in primary human hepatocytes (PHH) at day 11 (D11) post transfection (P-TF) with the indicated base editor systems, and maximum percent A to G base editing (right axis and right bar of each pair of bars) of a factor B polynucleotide measured in the PHH at day 13 (D13) P-TF with the indicated base editor systems. In **FIG. 5**, the listed editors are base editors containing the indicated TadA* adenosine deaminase domain, and the term “NHP X-Reactivity” means “non-human primate cross-reactivity.” A base editor system with NHP X-Reactivity will edit both a human a non-human primate factor B polynucleotide. The guide sg23 was used as a positive control. The guide polynucleotide gRNA1204 targeted the human factor B polynucleotide sequence GCTTACAATGACTGAGATCTTGG (SEQ ID NO: 429), which differs from the following non-human primate (cyno) factor B polynucleotide sequence at the G in bold:

GCTTACAG**T**GACTGAGATCTTGG (SEQ ID NO: 430). An Abcam Elisa Kit (Human Factor B ELISA Kit (ab137973)) was used to measure protein levels (Range: 4.375 ng/ml - 140 ng/ml; lower limit of quantitation (LLOQ): 0.8 ng/mL). In **FIG. 5**, the editor “spCas9” refers to an spCas9 endonuclease capable of inducing a double-stranded break of DNA.

FIG. 6 provides a bar graph showing the impact of guide polynucleotide spacer length on percent A to G base editing of a factor B polynucleotide in HEK293T cells. The cells were base edited using base editor systems containing the indicated adenosine deaminase base editor and the guide RNA with a spacer having the indicated nucleotide (nt) length ranging from 19 to 23 nucleotides. The first 5 bars from the left correspond to the base editor ABE8.8 with specificity for an NGG PAM sequence, the second 5 bars from the left correspond to the base editor ABE 8.13 with specificity for an NGG PAM sequence, the third 5 bars from the left correspond to the base editor ABE 8.8 with specificity for an NGG PAM sequence, and the rightmost bar corresponds to ABE8.8 with specificity for an NGG PAM sequence.

FIGs. 7A and 7B provide a bar graph and a schematic diagram relating to optimization of guide spacer length. **FIG. 7A** provides a bar graph showing human complement factor B (hCFB) protein levels (left axis and left bar of each pair of bars) in human hepatocytes isolated from a PXB-mouse (PXB cells) at day 11 (D11) post transfection (P-TF) with the indicated base editor systems, and maximum percent A to G base editing (right axis and right bar of each pair of bars) of a factor B polynucleotide measured in the PXB cells at day 13 (D13) P-TF with the indicated base editor systems. **FIG. 7A**, the listed editors are base editors containing the indicated TadA* adenosine deaminase domain, the term “NHP X-Reactivity” means “non-human primate cross-reactivity,” and the term “Protospacer Length(nt)” indicates the length (19-23 nucleotides) of the spacer in nucleotides (nt) corresponding to the indicated guide polynucleotides. A base editor system with NHP X-Reactivity will edit both a human a non-human primate factor B polynucleotide. The guide sg23 was used as a positive control. The guide polynucleotide gRNA1204 targeted the human factor B polynucleotide sequence GCTTACAATGACTGAGATCTTGG (SEQ ID NO: 429), which differs from the following non-human primate (cyno) factor B polynucleotide sequence targeted by the guide polynucleotide gRNA1999 (gRNA1204 non-human primate surrogate) at the G in bold: GCTTACAGTGACTGAGATCTTGG (SEQ ID NO: 430). An Abcam Elisa Kit (Human Factor B ELISA Kit (ab137973)) was used to measure protein levels (Range: 4.375 ng/ml - 140 ng/ml; lower limit of quantitation (LLOQ): 0.8 ng/mL). An Abcam Elisa Kit (Human Factor B ELISA Kit (ab137973)) was used to measure protein levels (Range: 4.375 ng/ml - 140 ng/ml; lower limit of quantitation (LLOQ): 0.8 ng/mL). **FIG. 7B** provides a schematic diagram describing the experiment used to gather the data presented in **FIG. 7A**. In **FIG. 7B**, the term “NGS” indicates next-generation sequencing.

FIGs. 8A and 8B provide bar graphs and a Western blot image showing complement factor B polynucleotide base editing efficiency measured in primary cyno hepatocytes (PCH) transfected with base editor systems containing an adenosine deaminase and one of the indicated guides, which were either non-human primate and human factor B cross-reactive or hon-human primate surrogate guide polynucleotides. **FIG. 8A** provides a bar graph showing maximum percent A to G base editing of a factor B polynucleotide measured in PCH transfected with base editor systems containing an adenosine deaminase and the indicated guide polynucleotides. The guide polynucleotide gRNA2072 targeted the human factor B polynucleotide sequence GCTTACAATGACTGAGATCTTGG (SEQ ID NO: 429), which differs from the following non-human primate (cyno) factor B polynucleotide sequence at the G in bold: GCTTACAGT**G**ACTGAGATCTTGG (SEQ ID NO: 430). The top panel of **FIG. 8B** provides a Western blot showing levels of factor B measured in monkey serum, PCH supernatant, humanized mice serum, and in an Abcam human complement factor B (CFB) ELISA standard using an anti-complement factor B monoclonal antibody (Ab-CFB). The lower panel of **FIG. 8B** provides a bar graph showing cyno CFB protein levels normalized to pre-treatment levels for cells corresponding to **FIG. 8A**.

FIGs. 9A-9D provide bar graphs and plots showing maximum percent A to G base editing of a factor B polynucleotide measured in primary human hepatocytes (PHH) or human hepatoma cells (HepG2 cells) transfected with base editor systems containing the indicated mRNAs encoding an adenosine deaminase and the indicated guide polynucleotides. The base editors encoded by the mRNA molecules referenced in the figures (e.g., m3534/MRNA3534) are described in **Table 9**. **FIG. 9A** provides a bar graph showing maximum percent A to G base editing of a factor B polynucleotide measured in PHH transfected with the indicated base editor systems. The base editor system sg23/m3534 was used as a positive control. **FIGs. 9B-9D** provide plots showing maximum percent A to G base editing of a factor B polynucleotide measured in HepG2 cells transfected with base editor systems containing different doses of the guide polynucleotides TSBTx3826, TSBTx3837, and TSBTx3935, respectively, and a constant dose of the indicated mRNA molecules encoding a base editor. The base editors encoded by the mRNA molecules referenced in the figures (e.g., MRNA3534) are described in **Table 9**.

FIGs. 10A and 10B provide bar graphs showing human complement factor B (hCFB) maximum percent A to G base editing, insertion/deletion (indel) mutation rates, and protein levels in FRGTM liver-humanized mice administered a base editor system containing the

guide polynucleotide gRNA1193 and an ABE8.8 adenosine deaminase base editor. **FIG. 10A** provides a bar graph showing hCFB maximum percent A to G base editing and indel mutation rates measured in FRGTM liver-humanized mice transfected with a base editor system containing an adenosine deaminase base editor and 2 mg/kg (mpk) or 0.3 mpk of the end-modified guide polynucleotide gRNA1193. The mice were administered tris buffered saline (TBS) as a negative control. **FIG. 10B** provides a bar graph showing concentrations (Conc.) of hCFB protein (hCFB Pr.) measured in FRGTM liver-humanized mice transfected with a base editor system containing an adenosine deaminase base editor and 2 mg/kg (mpk) of the end-modified guide polynucleotide gRNA1193. In **FIG. 10B**, each set of three bars corresponds, from left-to-right, to measurements taken at day 0 (D0) prior to transfection (i.e., “Predose”), at day 7 post-transfection, and at the end of the experiment (i.e., “Terminal”), which was day 14 post-transfection. The upper panel of **FIG. 10B** shows unnormalized protein concentrations and the lower panel of **FIG. 10B** shows protein concentrations normalized to day 0 (D0) concentrations.

FIG. 11 provides a set of plots showing a negative correlation between serum hC3 and hCFB protein levels in FRGTM liver-humanized mice transfected with a base editor system containing an ABE8.8 adenosine deaminase base editor and 2 mg/kg (mpk) or 0.3 mpk of the end-modified guide polynucleotide gRNA1193. The x-axis indicates the day post-transfection at which measurements were taken. In **FIG. 11**, the arrows extending from each curve indicate the axis to which each curve corresponds. The mice were administered tris buffered saline (TBS) as a negative control.

FIGs. 12A and 12B provide bar graphs showing human complement factor B (hCFB) percent A to G base editing (**FIG. 12A**) and protein levels (**FIG. 12B**) in FRGTM liver-humanized mice administered a base editor system containing the guide polynucleotide TSBTx3826 with an NLS nucleotide modification scheme and one of the indicated adenosine deaminase base editors (i.e., ABE8.8, ABE8.20, or ABE9.52). A base editor system containing the guide polynucleotide sg23 was used as a positive control. In **FIGs. 12A and 12B** the term “Mod Schem selection” indicates the nucleotide modification scheme of the guide polynucleotide, the term “BE selection (NLS)” indicates base editor selection using guide polynucleotides having an NLS nucleotide modification scheme, the term “Pre-dose” indicates a measurement taken prior to administration of the base editor system to the mice, and the terms “0.5 mpk” and “0.3 mpk” indicate the dose of guide polynucleotide administered to the mice. The TSBTx3826 guide polynucleotide was cross-reactive (i.e., targeted for base editing) both human and cyno CFB polynucleotides, and the location of the

target base edit was a splice site at the 5'-end of Exon 3 of the factor B polynucleotide. In **FIGs. 12A and 12B**, the term “ABE9.52” refers to a base editor containing the following adenosine deaminase domain: TadA*8.20 with the amino acid alterations V82T, Y147T, and Q154S.

5 **FIG. 13** provides a bar graph showing levels of the indicated human complement factor B (hCFB) exons in mRNA collected from tissues of FRGTM liver-humanized mice administered a base editor system containing the guide polynucleotide TSBTx3826 targeting a splice site at the 5'-end of Exon 10 and one of the indicated adenosine deaminase base editors. Measurements were taken at day 14 post-administration of the base editor system. In
10 **FIG. 13**, mRNA levels were normalized to mRNA levels measured for an actin beta (ACTB) gene. In **FIG. 13**, the term “ALAS1 (sg23)” indicates levels of 5'-Aminolevulinate Synthase 1 (ALAS1) transcripts in mice administered a base editor system containing the guide polynucleotide sg23. In **FIG. 13**, the term “ABE9.52” refers to a base editor containing the following adenosine deaminase domain: TadA*8.20 with the amino acid alterations V82T,
15 Y147T, and Q154S.

FIGs. 14A and 14B provide bar graphs showing human complement factor B (hCFB) percent A to G base editing (**FIG. 14A**) and protein levels (**FIG. 14B**) in FRGTM liver-humanized mice administered a base editor system containing the guide polynucleotide TSBTx3837 with an HM01 nucleotide modification scheme and one of the indicated
20 adenosine deaminase base editors (i.e., ABE8.8 or ABE8.20). Base editor systems containing the guide polynucleotide sg23 or TSBTx3826 having an NLS nucleotide modification scheme were used as controls. In **FIGs. 14A and 14B** the term “Mod Schem selection” indicates the nucleotide modification scheme of the guide polynucleotide, the term “BE selection (NLS)” indicates base editor selection using guide polynucleotides having an NLS
25 nucleotide modification scheme, the term “Pre-dose” indicates a measurement taken prior to administration of the base editor system to the mice, and the terms “0.5 mpk” and “0.3 mpk” indicate the dose of guide polynucleotide administered to the mice. The TSBTx3837 guide polynucleotide targeted hCFB and was not cross-reactive (i.e., targeted for base editing) cyno CFB polynucleotides because the TSBTx3837 guide polynucleotide target site differed from
30 the corresponding cyno CFB target site by one (1) nucleotide, and the location of the target base edit was a splice site at the 3'-end of Exon 11 of the factor B polynucleotide. In **FIGs. 14A and 14B**, the term “ABE9.52” refers to a base editor containing the following adenosine deaminase domain: TadA*8.20 with the amino acid alterations V82T, Y147T, and Q154S.

FIG. 15 provides a bar graph showing levels of the indicated human complement factor B (hCFB) exons in mRNA collected from tissues of FRGTM liver-humanized mice administered a base editor system containing the guide polynucleotide TSBTx3837 targeting a splice site at the 3'-end of Exon 11 and one of the indicated adenosine deaminase base editors. Measurements were taken at day 14 post-administration of the base editor system. In **FIG. 15**, mRNA levels were normalized to mRNA levels measured for an actin beta (ACTB) gene. In **FIG. 15**, the term "ALAS1 (sg23)" indicates levels of 5'-Aminolevulinate Synthase 1 (ALAS1) transcripts in mice administered a base editor system containing the guide polynucleotide sg23.

FIG. 16A and 16B provide bar graphs showing human complement factor B (hCFB) percent A to G base editing (**FIG. 16A**) and protein levels (**FIG. 16B**) in FRGTM liver-humanized mice administered a base editor system containing the guide polynucleotide TSBTx3835 with an end-mod nucleotide modification scheme and one of the indicated adenosine deaminase base editors (i.e., ABE8.13 or ABE9.52). Base editor systems containing the guide polynucleotide sg23 or TSBTx3826 having an NLS nucleotide modification scheme were used as controls. In **FIGs. 16A and 16B** the term "Mod Schem selection" indicates the nucleotide modification scheme of the guide polynucleotide, the term "BE selection (NLS)" indicates base editor selection using guide polynucleotides having an NLS nucleotide modification scheme, the term "Pre-dose" indicates a measurement taken prior to administration of the base editor system to the mice, and the terms "0.5 mpk" and "0.3 mpk" indicate the dose of guide polynucleotide administered to the mice. The TSBTx3835 guide polynucleotide targeted hCFB and was cross-reactive (i.e., targeted for base editing) with human and cyno CFB polynucleotides, and the location of the target base edit was a splice site at the 3'-end of Exon 16 of the factor B polynucleotide. In **FIGs. 16A and 16B**, the term "ABE9.52" refers to a base editor containing the following adenosine deaminase domain: Tada*8.20 with the amino acid alterations V82T, Y147T, and Q154S.

FIG. 17 provides a bar graph showing levels of the indicated human complement factor B (hCFB) exons in mRNA collected from tissues of FRGTM liver-humanized mice administered a base editor system containing the guide polynucleotide TSBTx3835 targeting a splice site at the 3'-end of Exon 16 and one of the indicated adenosine deaminase base editors. Measurements were taken at day 14 post-administration of the base editor system. In **FIG. 17**, mRNA levels were normalized to mRNA levels measured for an actin beta (ACTB) gene. In **FIG. 17**, the term "ALAS1 (sg23)" indicates levels of 5'-Aminolevulinate Synthase 1 (ALAS1) transcripts in mice administered a base editor system containing the guide

polynucleotide sg23. In **FIG. 17**, the term “ABE9.52” refers to a base editor containing the following adenosine deaminase domain: TadA*8.20 with the amino acid alterations V82T, Y147T, and Q154S.

FIG. 18 provides a plot showing complement factor B polynucleotide maximum percent A to G editing in primary human hepatocytes (PHH) or primary cyno hepatocytes (PCH), as indicated, transfected with base editor systems containing the indicated guide polynucleotides and an adenosine deaminase base editor. A base editor system containing an adenosine deaminase and the guide polynucleotide sg23 was used as a positive control. Cells were transfected with the guide polynucleotide and mRNA encoding the base editor at a mass ratio of 1-to-3 (1:3). The TSBTx3837 guide was used in combination with the base editor ABE8.20, and the guide had an HM01 nucleotide modification scheme. The TSBTx3826 guide was used in combination with a base editor containing a TadA*8.20 adenosine deaminase domain with the amino acid alterations V82T, Y147T, and Q154S, and the guide had an NLS nucleotide modification scheme.

FIGs. 19A-19D provide a schematic diagram and plots. **FIG. 19A** provides a schematic diagram showing the sequence of a polynucleotide construct used to compare the potency of guide polynucleotides targeting human complement factor B (CFB) and/or non-human primate CFB for base editing. The binding sites for guide polynucleotides targeting a human CFB polynucleotide (i.e., “CFB guide-human”) and a non-human primate CFB polynucleotide (i.e., “CFB guide-NHP”) are indicated. In **FIG. 19A**, the term “10bp” indicates a 10 nucleotide spacer, and the term “30 bp random spacer” indicates a randomized sequence of 30 nucleotides. In **FIG. 19A**, the two nucleotide sequences depicted are reverse complements of one another. In **FIG. 19A**, the upper nucleotide sequence is:
 CATGGCAGGCCAAGATCTCAGTCATTGTAAGCACAGAATCCCATATGGAAGGTCATTAGCTC
 CGGCAAGCAATCATGGCAGGCCAAGATCTCAGTCACTGTAAGCACAGAATCCCA (SEQ ID NO: 431), and the amino acid sequences are HGRPRSQSL (SEQ ID NO: 432) and AQNPIWKVISSGKQSWQAKISVTVSTES (SEQ ID NO: 433). The term “*” in the amino acid sequence of **FIG. 19A** indicates a stop codon, and the term “CFB insert” indicates that the polynucleotide construct was inserted into the genome of HEK293T cells. **FIGs. 19B-19D** show percent base editing in three separate experiments (i.e., Batch 1, Batch 2, and Batch 3, respectively) at the “CFB guide-human” and “CFB guide-NHP” sites in HEK293T cells transfected with base editor systems containing an adenosine deaminase and the indicated

doses of the guide gRNA2067 (TSBTx3837; targeting the CFB guide-human site) or the guide gRNA2072 (TSBTx2072; targeting the CFB guide-HNP site).

FIG. 20 provides a bar graph showing complement factor B (CFB) TATA box A to G editing in human hepatoma cells (HepG2 cells) transfected with the indicated base editor systems (i.e., Sample 1 to Sample 16, which are described in **Table 12.1A**) containing a guide polynucleotide and an adenosine deaminase. The cells were transfected with a saturating dose of 800 ng total of guide polynucleotide and mRNA encoding the base editor at a mass ratio of 1:3. The CFB TATA box was located at positions -157 to -151 relative to the CFB start codon. A base editor system containing an adenosine deaminase base editor and the guide sgRNA_088 (sg23) was used as a positive control. The bars of **FIG. 20** each correspond in order, from left-to-right, to base editor systems containing the base editors listed in **Table 12.1A**.

FIGs. 21A and 21B provide bar graphs showing complement factor B (CFB) start codon A to G editing in human hepatoma cells (HepG2 cells) (**FIG. 21A**) or primary human hepatocyte (PHH) monolayer cells transfected with base editor systems (i.e., Sample 1 to Sample 8 of **FIG. 21A** and Sample 1 to Sample 3 of **FIG. 21B**, which are described in **Table 12.1B**) containing a guide polynucleotides and an adenosine deaminase. A base editor system containing an adenosine deaminase base editor and the guide sgRNA_088 (sg23) was used as a positive control. Beneath the x-axis of the bar graphs of **FIGs. 21A and 21B** are listed the CFB amino acid alterations (e.g., M1T, G2E, G2R, L5P, or S3P) corresponding to the base edits corresponding to each bar. The cells were transfected with a saturating dose of 800 ng total of guide polynucleotide and mRNA encoding the base editor at a mass ratio of 1:3.

FIGs. 22A and 22B provide a bar graph and a schematic diagram relating to complement factor B (CFB) TATA-box and start codon disruption in primary human hepatocytes (PHH) for protein knock-down. **FIG. 22A** provides a bar graph showing human complement factor B (hCFB) protein levels (left axis and left bar of each pair of bars) in PHH at day 12 (D12) post transfection (P-TF) with base editor systems (i.e., Sample 1 to Sample 16, which are described in **Table 12.1C**) containing an adenosine deaminase and a guide polynucleotide, and maximum percent A to G base editing (right axis and right bar of each pair of bars) of a factor B polynucleotide measured in the PXB cells at day 13 (D13) P-TF with the base editor systems. **FIG. 22A**, a base editor system containing an adenosine deaminase and the guide polynucleotide sgRNA_088 (sg23) was used as a positive control for base editing. **FIG. 22B** provides a schematic diagram describing the experiment used to gather the data presented in **FIG. 22A**. In **FIG. 22B**, the term “MC” indicates a media

change, and the term “NGS” indicates next-generation sequencing. The data of **FIG. 22A** is not normalized; however, a similar pattern was observed with data normalization to protein levels prior to transfection (i.e., day 0).

FIG. 23 provides a set of bar graphs showing high editing and good reduction of complement factor B (CFB) protein levels in primary human hepatocyte (PHH) co-cultures transfected with base editor systems containing an adenosine deaminase with one of the indicated PAM specificities (e.g., NGC, NGG, or NGA) and one of the indicated guide polynucleotides targeting the CFB start codon for base editing. Base editor systems containing an adenosine deaminase and the guide polynucleotide sg23 or gRNA1193 (TSBTx3826) were used as a positive control. In **FIG. 23**, the term “dABE (-) Control” indicates a defective or “dead” adenosine base editor. The top panel of **FIG. 23** presents data collected using cells from a donor designated “JGC” and the lower panel of **FIG. 23** presents data collected using cells from a donor designated “MRW.” The base editor systems were administered to the cells at a saturating total dose of 800 ng of the guide polynucleotide and mRNA encoding the adenosine deaminase. None of the guide polynucleotides were cross-reactive with non-human primate target sites (i.e., the guides target a human CFB polynucleotide for base editing but not a cyno CFB polynucleotide). The target site for gRNA 3657 was TGCTCCCCATGGC**GTTGGAAGGC** (SEQ ID NO: 434), whereas the corresponding non-human primate (NHP) target site is TGCTCCCCATGGC**ATTAGAAGGC** (SEQ ID NO: 435), where bold nucleotides indicate where the human gRNA 3657 target site differs from the corresponding NHP target site, and where the nucleotides corresponding to the CFB start codon are underlined. The target site for gRNA 3658 was **TTGCTCCCCATGGC**GTTGGAAGG (SEQ ID NO: 436), whereas the corresponding non-human primate (NHP) target site is **CTGCTCCCCATGGC**ATTAGAAGG (SEQ ID NO: 437), where bold nucleotides indicate where the human gRNA 3658 target site differs from the corresponding NHP target site, and where the nucleotides corresponding to the CFB start codon are underlined. The target site for gRNA 3660 was CCCCATGGC**GTTGGAAGGCAGGA** (SEQ ID NO: 438), whereas the corresponding non-human primate (NHP) target site is CCCCATGGC**ATTAGAAGGCAGGA** (SEQ ID NO: 439), where bold nucleotides indicate where the human gRNA 3660 target site differs from the corresponding NHP target site, and where the nucleotides corresponding to the CFB start codon are underlined. In **FIG. 23**, for every set of three bars, the first two bars from the left correspond to hCFB protein level measurements taken at day 7 (D7) and day 13 (D13) post-transfection and normalized to levels measured prior to transfection (i.e., at day

0), and the bar on the right corresponds to CFB polynucleotide A to G editing measured at day 13.

FIG. 24 provides a schematic diagram showing guide-dependent and guide-independent deamination of a nucleotide of a polynucleotide and lists representative methods by which the same may be predicted or measured. **FIG. 24** is adapted from Kempton and Lei, *Science*, 364:234-236 (2019), the disclosure of which is incorporated herein by reference in its entirety for all purposes.

FIG. 25 provides a bar graph showing an alternative presentation of data from **FIG. 23** relating to start codon disruption of CFB in primary human hepatocyte co-cultures. In **FIG. 25**, each pair of bars represents, from left-to-right, hCFB protein level and A to G editing. In **FIG. 25**, “dABE (-) Ctrl” indicates negative control base editor systems containing a catalytically inactive base editor. The base editor systems of **FIG. 25** (i.e., Sample 1 to Sample 9) are described in **Table 12.1D**.

FIGs. 26A and 26B provide a bar graph and a schematic diagram relating to a functional assessment of start codon targeting guides in a long-term HepG2 culture system. **FIG. 6** provides a bar graph showing base editing rates for the indicated target sites achieved using the indicated active or inactive base editor systems corresponding to Sample 1 to Sample 8, which are described in **Table 12.1E**. **FIG. 26B** provides a schematic diagram describing the experiment used to collect the data presented in **FIG. 26A**. In **FIG. 26B**, “MC” indicates a media change, “TF” indicates transfection with a base editor system, and “NGS” indicates next-generation sequencing.

FIG. 27 provides plots showing human complement factor B (hCFB) protein levels in long-term HepG2 culture systems containing cells transfected with the indicated active (left panel) or inactive (right panel) base editor systems corresponding to Sample 1 to Sample 8, which are described in **Table 12.1E**, and targeting the indicated sites for editing at the indicated days post-transfection (post-TF). In the left panel of **FIG. 27**, the lines at 10-days post-TF correspond, from top-to-bottom, to Sample 1, Sample 7, Sample 2, Sample 6/Sample 5, Sample 3, and Sample 4, and the third line from the bottom at 22 days corresponds to Sample 5. In the right panel of **FIG. 27**, the lines at 10-days post-TF correspond, from top-to-bottom, Sample 1, Sample 6, Sample 2, Sample 3, Sample 7, Sample 4, and Sample 5. “Inactive editors” contained a catalytically inactive base editor.

DETAILED DESCRIPTION

Provided herein are base editors, endonucleases, and guide RNAs (gRNAs) for use in editing, modifying, or altering a target polynucleotide. In particular embodiments, a base editor or endonuclease of the present disclosure modifies a complement factor B (CFB) polynucleotide. In particular embodiments, a base editor of the invention introduces a stop codon alteration in a CFB polynucleotide or disrupts a TATA box, start site, or splice site in the CFB polynucleotide. The alterations are associated with a reduction in activity or levels of a CFB polypeptide and/or polynucleotide in a cell.

The invention of the disclosure is based, at least in part, on the discovery that the alternative pathway of the complement system requires the protein factor B for complement pathway amplification and function. The invention is further based, at least in part, upon the discovery that base editing (e.g., disruption of splice acceptor or splice donor, or introduction of a stop codon) can be used to reduce the expression of a factor B polypeptide in a cell associated with a dysregulated complement system (e.g., inappropriate activation). In particular, reducing activity and/or expression of the factor B polypeptide in a subject diagnosed with a disease or disorder associated with over-activation of the complement system can be an effective treatment strategy. This reduction in activity and/or expression can be effected using any of the base editing systems and/or endonucleases and methods provided herein. Accordingly, the invention features compositions and methods for editing a factor B polynucleotide. The edit to the factor B polynucleotide is associated with a reduction in expression and/or activity of a factor B polypeptide in a cell, tissue, and/or body fluid of a subject, as well as a reduction in symptoms associated with overactivation or otherwise pathogenic activation of the complement system in a subject.

Accordingly, as described in the examples provided herein base editor systems were successfully developed to disrupt complement system activity through functional disruption of factor B at the gene level. Factor B disruption was carried out through silencing/knock-out of the factor B gene.

In embodiments, the methods of the present disclosure include disrupting splicing of a factor B polynucleotide transcript. For example, the base editors or base editor systems provided herein can be used for editing a nucleobase in the splice acceptor situated 5' of an exon of the factor B polynucleotide. In some embodiments, the target sequence is a splice acceptor in a portion of an intron adjacent to an exon of the factor B polynucleotide and editing a nucleobase in the splice acceptor is associated with a change in the splice acceptor compared to a wild-type splice acceptor site. In some embodiments, the deamination of an A

or C nucleobase in the splice acceptor results in disruption of splicing of the mRNA transcript during or after transcription. In some embodiments, the subject has or has the potential to develop a dysregulated and/or over-activated complement system and any disease or disorder associated therewith.

5 In some instances, the methods of the present disclosure include modifying a factor B polynucleotide to introduce a stop codon, start site disruption, or TATA box disruption associated with a reduction in levels or activity of the complement factor B polynucleotide and/or polypeptide. The alterations can be effected by a base editor system, such as those described herein.

10 In some embodiments, the present disclosure provides base editors that efficiently generate an intended mutation, such as a point mutation, in a nucleic acid molecule (*e.g.*, a nucleic acid within a genome of a subject) without generating a significant number of unintended mutations, such as unintended point mutations. In some embodiments, an intended mutation is a mutation that is generated by a base editor system containing a specific
15 base editor (*e.g.*, an adenosine base editor or a cytidine base editor), where the base editor system is specifically designed to generate the intended mutation. In some embodiments, the intended mutation is an adenine (A) to guanine (G) point mutation within the non-coding region of a gene. In some embodiments, the intended mutation is a cytosine (C) to thymine (T) point mutation within the non-coding region of a gene. In some embodiments, the
20 intended mutation is a mutation of a splice acceptor in an intron of a gene associated with a disease or disorder. In some cases, the intended mutation is an indel mutation. In some embodiments, the intended mutation is an adenine (A) to guanine (G) point mutation in the splice acceptor site in an intron of a gene associated with a disease or disorder. The intended mutation can include the introduction of a stop codon to a polynucleotide sequence. In some
25 embodiments, the intended mutation is a mutation that disrupts normal splicing of a complete transcript of a gene, for example, an A to G change in a splice acceptor site within an intron of a disease-causing or a disease-associated gene. In some embodiments, the intended mutation is a mutation in a splice acceptor site that disrupts splicing of a gene transcript and results in an alternative transcript that encodes a truncated and/or nonfunctional protein
30 product.

 In some embodiments, any of the base editors or endonucleases provided herein are capable of generating a ratio of intended mutations to unintended mutations (*e.g.*, intended point mutations : unintended point mutations) that is greater than 1 : 1. In some embodiments, any of the base editors provided herein are capable of generating a ratio of

intended mutations to unintended mutations (*e.g.*, intended point mutations : unintended point mutations) that is at least 1.5: 1, at least 2: 1, at least 2.5: 1, at least 3: 1, at least 3.5: 1, at least 4: 1, at least 4.5: 1, at least 5: 1, at least 5.5: 1, at least 6: 1, at least 6.5: 1, at least 7: 1, at least 7.5: 1, at least 8: 1, at least 10: 1, at least 12: 1, at least 15: 1, at least 20: 1, at least 25: 1, at least 30: 1, at least 40: 1, at least 50: 1, at least 100: 1, at least 150: 1, at least 200: 1, at least 250: 1, at least 500: 1, or at least 1000: 1, or more.

In some embodiments, editing of a plurality of nucleobase pairs in one or more genes using the methods provided herein results in formation of at least one intended mutation. In some embodiments, the formation of the at least one intended mutation is in a splice acceptor site and results in disruption of splicing of the mRNA transcript of a disease-associated gene. In some embodiments, the formation of the at least one intended mutation results in a reduction in activity and/or expression of a disease-associated gene. It should be appreciated that multiplex editing can be accomplished using any method or combination of methods provided herein.

The present disclosure provides methods for the treatment of a subject diagnosed with a dysregulated and/or over-activated complement system or any disease or disorder associated therewith. For example, in some embodiments, a method is provided that comprises administering to a subject having or having a propensity to develop a dysregulated and/or over-activated complement system, an effective amount of a nucleobase editor (*e.g.*, an adenosine deaminase base editor or a cytidine deaminase base editor) to effect an alteration in a factor B polynucleotide sequence.

THE COMPLEMENT SYSTEM AND FACTOR B

Complement is a system consisting of numerous plasma and cell-bound proteins that plays an important role in both innate and adaptive immunity. The proteins of the complement system act in a series of enzymatic cascades through a variety of protein interactions and cleavage events.

The complement system is a component of the innate immune system and is important for the clearance of pathogens and dead or dying cells. Complement activation results in: formation of a membrane attack complex and cell cytolysis; opsonization of foreign material, targeting it for phagocytosis; and activation of inflammation and diverse immune components. Many complement components are circulating factors primarily produced in the liver.

The complement system plays an important role in defending the body against infectious agents. The complement system contains over 30 serum and cellular proteins that are involved in three major pathways, known as the classical, alternative, and lectin pathways. The classical pathway is typically triggered by binding of a complex of antigen and IgM or IgG antibody to C1 (though certain other activators can also initiate the pathway).
5 Activated C1 cleaves C4 and C2 to produce C4a and C4b, in addition to C2a and C2b. C4b and C2a combine to form C3 convertase, which cleaves C3 at a defined cleavage site to form C3a and C3b. Binding of C3b to C3 convertase produces C5 convertase, which cleaves C5 into C5a and C5b. C3a, C4a, and C5a are anaphylotoxins and mediate multiple reactions in
10 the acute inflammatory response. C3a and C5a are also chemotactic factors that attract immune system cells such as neutrophils. Further details relating to C3 are provided in Ricklin, *et al.* "Complement component C3 - The 'Swiss Army Knife' of innate immunity and host defense." *Immunol Rev.* 2016 Nov; 274(1):33-58; and in Janssen, *et al.*, "Structures of complement component C3 provide insights into the function and evolution of immunity."
15 *Nature.* 2005 Sep 22;437(7058):505-11, the disclosures of which are incorporated herein by reference in their entireties for all purposes.

The alternative pathway (see, e.g., **FIG. 1**) is typically initiated by and amplified at microbial surfaces and various complex polysaccharides. The alternative pathway is triggered by the covalent binding of C3b to a pathogen or cell surface. Next, factor B binds to surface
20 bond C3b, making it susceptible to plasma factor D cleavage. The result is production of Ba and active protease Bb, which remains bound to C3b creating C3bBb, which is the C3 convertase of the alternative complement pathway. This starts the amplification loop with the C3 convertase generating more C3b on the cell surface and the process repeats. Ultimately, there is C3b saturation on the cell surface with release of C3a, a small inflammatory
25 mediator. Eventually, some of the C3b binds to preexisting C3 convertase producing C3b2Bb, which is the alternative pathway's C5 convertase. This cleaves C5 into C5b, which generates the membrane attack complex (MAC), and C5a, a potent proinflammatory mediator. Complement-mediated endothelial cell injury creates a prothrombotic state. It exposes subendothelial collagens and releases vWF and fibrinogen formation. Normally the
30 presence of complement regulatory proteins on cell surfaces prevents significant complement activation from occurring thereon. A more detailed description of the alternative pathway is provided in Keir, L. and Coward, R.J.M., 2011. *Pediatr. Nephrol.* 26, 523–533, the disclosure of which is incorporated herein by reference in its entirety for all purposes.

Complement factor B (CFB; alternatively “factor B”) is a serine protease and a key component of the complement alternative pathway (AP)/amplification loop. Complement factor D (CFD), another serine protease, cleaves CFB to form Ba and Bb. Bb forms an integral part of the convertase complexes of the AP, which serve to activate the central complement proteins C3 and C5 through proteolytic cleavage.

The C5 convertases produced in both pathways cleave C5 to produce C5a and C5b. C5b then binds to C6, C7, and C8 to form C5b-8, which catalyzes polymerization of C9 to form the C5b-9 membrane attack complex (MAC), also known as the terminal complement complex (TCC). The MAC inserts itself into target cell membranes and causes cell lysis.

Small amounts of MAC on the membrane of cells may have a variety of consequences other than cell death. If the TCC does not insert into a membrane, it can circulate in the blood as soluble sC5b-9 (sC5b-9). Levels of sC5b-9 in the blood may serve as an indicator of complement activation.

The lectin complement pathway can be initiated by binding of mannose-binding lectin (MBL) and MBL-associated serine protease (MASP) to carbohydrates. The MB1-1 gene (known as LMAN-1 in humans) encodes a type I integral membrane protein localized in the intermediate region between the endoplasmic reticulum and the Golgi. The MBL-2 gene encodes the soluble mannose-binding protein found in serum. In the human lectin pathway, MASP-1 and MASP-2 are involved in the proteolysis of C4 and C2, leading to a C3 convertase described above.

Accordingly, the present disclosure provides methods for disrupting complement activation by altering a polynucleotide encoding factor B.

DISEASES AND/OR DISORDERS ASSOCIATED WITH UNDESIRABLY INCREASED ACTIVATION OF THE COMPLEMENT SYSTEM

Inappropriate activation of the complement system can lead to various diseases and/or disorders in a subject. For example, inappropriate activation of the complement system in a subject damages cells resulting in increased inflammation, the presence of autoantibodies, neural degeneration, and microthrombosis, among others. Inappropriate activation of the complement system is associated with damage to the nervous system (e.g., the Central Nervous System (CNS)), circulatory system, kidneys, eyes, blood cells (e.g., red and white blood cells and platelets), and transplanted organs, as well as damage to other organs or tissues, which may be associated with the presence of micro-emboli. Therefore, an effective treatment for such diseases and/or disorders can involve altering a factor B nucleotide

sequence to reduce and/or eliminate expression and/or activity of a factor B polypeptide in a subject, thereby reducing activation of the complement system in an organ, cell, and/or tissue. In embodiments, the organ or tissue is an eye, kidney, nervous system component, heart, or thyroid. Not intending to be bound by theory, complement protein levels in the eye may be
5 dependent on circulating levels of complement proteins generated in the liver.

Some important indications for a subject requiring treatment for inappropriate activation (e.g., overactivation or dysregulation) of the complement system include paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), and IC-MPGN/C3 glomerulopathy. PNH is associated with hemolysis of red blood cells
10 (RBCs) resulting in anemia and thrombosis. The disorder aHUS is associated with hemolysis of RBCs as well as thrombocytopenia and acute kidney failure caused by abnormal clot formation in small blood vessels in the kidney. IC-MPGN and C3 glomerulopathy are associated with kidney malfunction and end-stage renal disease caused by damage to glomeruli of the kidney.

Non-limiting examples of diseases associated inappropriate activation of the complement system include blood disorders, transplant or graft rejection, inflammatory diseases or disorders, eye diseases or disorders, kidney diseases or disorders, heart disorders, respiratory/pulmonary diseases or disorders, autoimmune disorders, inflammatory bowel diseases or disorders, arthritis, neurodegenerative diseases or disorders, musculoskeletal
20 diseases or disorders associated with inflammation, disorders affecting the integumentary system, diseases or disorders affecting the central nervous system, diseases or disorders affecting the circulatory system, diseases or disorders affecting the gastrointestinal system, diseases or disorders affecting the thyroid, chronic pain, allergies, and pulmonary diseases. Further non-limiting examples of diseases associated with inappropriate activation of the
25 complement system include acute antibody-mediated rejection, age-related macular degeneration (e.g. wet or dry age-related macular degeneration), allergic asthma, allergic bronchopulmonary aspergillosis, allergic neuritis, allergic rhinitis, Alzheimer's disease, amyotrophic lateral sclerosis, anaphylaxis, atopic dermatitis, atypical hemolytic syndrome (aHUS), autoimmune diseases, autoimmune hemolytic anemia, Bechet's disease, Behcet's
30 disease, bronchiolitis, bronchiolitis obliterans, C3 glomerulopathy, cancer, central nervous system (CNS) inflammatory disorders, choroidal neovascularization (CNV), choroiditis, chronic allograft vasculopathy, chronic hepatitis, chronic inflammation, chronic inflammatory diseases, chronic muscle inflammation, chronic pain, chronic pancreatitis, chronic rejection of a transplant or graft, chronic urticaria, Churg-Strauss syndrome,

conjunctivitis, COVID-19, cyclitis, demyelinating diseases, dermatitis, dermatomyositis, diabetic retinopathy, diseases of the circulatory system, disorders associated with excessive or inappropriate activity of IgE-producing cells, disorders associated with high levels or inappropriate activity of CD4+ helper T cells of the Th17 subtype, encephalitis, eosinophilic pneumonia, eye disorders, geographic atrophy, giant cell arteritis, gingivitis, glaucoma, glomerulonephritis, glomerulonephritis (e.g., membranoproliferative glomerulonephritis or membranous glomerulonephritis), graft rejection or failure, GPA/MPA (granulomatosis with polyangiitis, microscopic), HELLP syndrome, Henoch-Schonlein purpura, hepatitis (e.g. hepatitis C), Huntington's disease, hyperacute rejection, hypersensitivity pneumonitis, idiopathic pulmonary fibrosis (IPF), IgA nephropathy (IgAN), inflammatory bowel diseases (e.g. Crohn's disease or ulcerative colitis), inflammatory joint conditions (e.g. arthritis such as rheumatoid arthritis or psoriatic arthritis, juvenile chronic arthritis, spondyloarthropathies Reiter's syndrome, or gout), inflammatory skin diseases, infusion reaction, interstitial pneumonia, iridocyclitis, iritis, ischemia/reperfusion injury, Kawasaki disease, keratitis, lupus nephritis, membranoproliferative glomerulonephritis (MPGN) (e.g. MPGN type I, type II, or type III), meningitis, microscopic polyangiitis, multiple sclerosis (MS), myasthenia gravis, myocarditis, nasal polyposis, neurodegenerative diseases, neuromyelitis optica, neuromyelitis optica (NMO), neuropathic pain, ocular inflammation, osteoarthritis, pancreatitis, panniculitis, Parkinson's disease, paroxysmal nocturnal hemoglobinuria (PNH), pars planitis, pathologic immune responses to tissue/organ transplantation, pemphigoid, pemphigus, periodontitis, persistent asthma, polyarteritis nodosa, polymyositis, primary membranous nephropathy, proliferative vitreoretinopathy, proteinuria, psoriasis, pulmonary fibrosis (e.g. idiopathic pulmonary fibrosis), radiation-induced lung injury, renal disease, respiratory disease or disorders (e.g. asthma or chronic obstructive pulmonary disease (COPD), or idiopathic pulmonary fibrosis, or asthma), respiratory distress syndrome, retinal neovascularization (RNV), retinopathy of prematurity, rheumatoid arthritis (RA), rhinosinusitis, sarcoid, sarcoidosis, scleritis, scleroderma, sclerodermatomyositis, sclerosis, sepsis, Sjögren syndrome, Sjoren's syndrome, stroke, systemic lupus erythematosus, systemic scleroderma, Takayasu's arteritis, Th2-associated disorders (e.g. a disorder associated with high levels or high activation of CD4+ helper T cells of the Th2 subtype), thyroiditis (e.g. Hashimoto's thyroiditis, Graves' disease, or post-partum thyroiditis), thyroiditis, transplant damage, transplant rejection, ulcerative colitis, uveitis, vasculitis, and Wegener's granulomatosis. In embodiments, the methods of the invention involve reducing complement-mediated hemolysis in a subject. Further non-limiting examples of diseases include

Creutzfeldt-Jakob disease, Pick's disease, mild cognitive impairment, fibromyalgia, frontotemporal dementia, dementia with Lewy bodies, multiple system atrophy, chronic inflammatory, demyelinating polyneuropathy, Guillain-Barré syndrome, multifocal motor neuropathy, non-alcoholic fatty liver disease (NAFLD) e.g., non-alcoholic steatohepatitis (NASH), and Stargardt macular dystrophy. Paroxysmal nocturnal hemoglobinuria is associated with mutations in *PigA* (Phosphatidyl inositol glycan anchor biosynthesis class a) that prevent GPI-anchor production and attachment of CD59 and CD55 to red blood cells (RBCs), which leads to the lysis of RBCs.

In some embodiments, inappropriate activation of the complement system is implicated in the progression and pathogenesis of a disease selected from glaucoma, diabetic retinopathy, age-related macular degeneration, and neurological diseases such as amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), Alzheimer's disease, and various Tauopathies.

Existing treatments for diseases associated with inappropriate activation of the complement system often require regular, sometimes invasive, dosing regimens. There is, therefore, a present need for improved treatments for diseases associated with inappropriate activation of the complement system.

The methods and compositions of the present disclosure are suitable in embodiments for use in treatment of any of the above-listed diseases or disorders related to improper activation of the complement system. In various instances, the methods involve introducing a modification to a factor B polynucleotide that results in reduced expression and/or activity of a factor B polypeptide in a cell.

EDITING OF TARGET GENES

Exemplary spacer sequences and guide polynucleotide sequences suitable for use in guide RNAs that can be used to produce the polynucleotide edits described herein (e.g., introduction of stop codons, splice-site disruption mutations, TATA box alterations, start codon alterations, etc.) are listed in **Tables 1A to 2F** below. To produce the polynucleotide edits, cells (e.g., cells in or from a subject) are contacted with one or more guide RNAs containing one or more of the spacer sequences listed in **Tables 2A to 2F** below, or fragments thereof, and a nucleobase editor polypeptide or complex containing a nucleic acid programmable DNA binding protein (napDNAbp) and one or more deaminases with cytidine deaminase and/or adenosine deaminase activity (e.g., a "dual deaminase" which has cytidine and adenosine deaminase activity). In embodiments, the base editor and/or endonuclease is

introduced to the cell using a polynucleotide sequence (e.g., mRNA) encoding the base editor and/or endonuclease. **Tables 1A to 1F** below list representative guide polynucleotide sequences suitable for use in methods of the disclosure for altering a CFB polynucleotide.

Tables 2A to 2F below list representative guide RNA spacer sequences that may be used in various embodiments in combination with indicated base editors. In embodiments, guide RNAs containing the spacer sequences listed in **Tables 2A to 2F** may be used to target the target sequences listed in **Tables 2A to 2F**, optionally to effect the edits (e.g., amino acid or nucleotide alterations) listed in any of **Tables 2A to 2F**. In some instances, the gRNA is added directly to a cell. In some embodiments, the gRNA comprises nucleotide analogs.

These nucleotide analogs can inhibit degradation of the gRNA from cellular processes. **Tables 2A to 2F** provide target sequences to be used for gRNAs. Further exemplary spacer sequences suitable for use in gRNA sequences for use in the methods provided herein include fragments of any of the spacers provided in **Tables 2A to 2F** as well as any of the spacers provided in **Tables 2A to 2F** modified to include an extension or truncation at the 3' and/or 5' end(s). In embodiments, a spacer sequence of **Tables 2A to 2F** can be modified to include a 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotide extension or truncation at the 3' and/or 5' end(s).

Variants of the spacer sequences provided herein comprising 1, 2, 3, 4, or 5 nucleobase alterations are contemplated. For example, variation of a target polynucleotide sequence within a population (e.g., single nucleotide polymorphisms) may require said alterations to a spacer sequence to allow the spacer to better bind a variant of a target sequence in a subject.

In various instances, it is advantageous for a spacer sequence to include a 5' and/or a 3' "G" nucleotide. In some cases, for example, any spacer sequence or guide polynucleotide provided herein comprises or further comprises a 5' "G", where, in some embodiments, the 5' "G" is or is not complementary to a target sequence. In some embodiments, the 5' "G" is added to a spacer sequence that does not already contain a 5' "G." For example, it can be advantageous for a guide RNA to include a 5' terminal "G" when the guide RNA is expressed under the control of a U6 promoter or the like because the U6 promoter prefers a "G" at the transcription start site (*see* Cong, L. *et al.* "Multiplex genome engineering using CRISPR/Cas systems. *Science* 339:819-823 (2013) doi: 10.1126/science.1231143). In some cases, a 5' terminal "G" is added to a guide polynucleotide that is to be expressed under the control of a promoter but is optionally not added to the guide polynucleotide if or when the guide polynucleotide is not expressed under the control of a promoter.

In some embodiments, a guide polynucleotide of the disclosure contains a spacer and scaffold containing one of the following nucleotide modification schemes (“mod schemes”), where “N” represents any nucleotide, “mN” indicates a 2'-OMe modification of the nucleotide “N”, and “Ns” indicates that the nucleotide “N” is linked to the following

5 nucleotide by a phosphorothioate (PS):

End-mod SpCas9 guide polynucleotide

mNsmNsmNsNNNNNNNNNNNNNNNNNNNGUUUAGAGCUAGAAAUAGCAAGUAAAAUAAGGCU
AGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU (SEQ ID NO:

10 440)

End-mod SaCas9 guide polynucleotide

mNsmNsmNsNNNNNNNNNNNNNNNNNNNGUUUAGUACUCUGUAAUGAAAAUUACAGAAUCUA
CUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU

15 (SEQ ID NO: 441)

HM01:

mNsmNsmNsNNNNNNNNNNNNNNNNNNNGUUUAGAmGmCmUmAmGmAmAmUmAmGmCAAGU
UAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmG
20 mAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NO: 440)

HM07:

mNsmNsmNsmNmNmNmNmNmNmNNNNNNNNNNNmGUUUAGmAmGmCmUmAmGmAmAmUm
AmGmCmAmAGUUmAAmAAmUAmAmGmGmCmUmAGUmCmCGUUmUmCAAmCmUmUmGmAmAm
25 AmAmAmGmUmGGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NO:
440)

NLS (bpsv40):

mNsmNsmNsNNNNNNNNNNNNNNNNNNNGUUUAGAGCUAGAAAUAGCAAGUAAAAUAAGGCU
30 AGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsmU-NHC6-CrossL-
ac- CKRTADGSEFESPKKRV (SEQ ID NOs: 440 and 446)

LONGEST:

mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUUAGAmGmCmCmGmGmCmGmGmAmAmAmCmGmC
mCmGmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGUGmG
mCmAmCmCmGmAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NO: 444)

5

NLS + LONGEST :

mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUUAGAmGmCmCmGmGmCmGmGmAmAmAmCmGmC
mCmGmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmG
mGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmUsmUsmUsmU-NHC5-CrossL-

10 CKRTADGSEFESPKKRKV (SEQ ID NOs: 445 and 446)

LONGEST + GOLD:

mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUUAGAmGmCmCmGmGmCmGmGmAmAmAmCmGmC
mCmGmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUmCAAmCmUmUGGACUUCGGUCCmAmAm

15 GUGGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NO: 447)

In embodiments, any of the above guide sequences, the number of N nucleotides (i.e., the spacer sequence) can vary between 15 and 25. In some cases, the number of N nucleotides is 18, 19, 20, 21, 22, or 23.

Exemplary guide RNA sequences are provided in the following **Tables 1A-1F and 20 2A-2F**. Throughout the tables, the ranges (e.g., 3-9) in the guide polynucleotide names indicate the base editing window for an exemplary base editor suitable for use with the guide polynucleotide (e.g., nucleotides 3 to 9, where location 1 is the first nucleobase complementary to the spacer and adjacent to the protospacer adjacent motif).

25 **Table 1A: Representative sequences for guide polynucleotides for use in guiding a base editor to alter a complement factor B splice site.¹**

Guide polynucleotide name	Guide polynucleotide sequence	SEQ ID NO
gRNA2055	mCsmUsmCsAGAUGUCUAUGUGUUUGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGG UGCUsmUsmUsmU	448
gRNA1193	mCsmCsmUsCAGAUGUCUAUGUGUUUGUUUUAGAGCUAGAAAUAGCAAG UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCG GUGCUsmUsmUsmU	449

¹ “mN” indicates a 2'-OMe modification of the nucleotide “N”, and “Ns” indicates that the nucleotide “N” is linked to the following (i.e., 3') nucleotide by a phosphorothioate (PS).

gRNA2057	mCsmCsmCsUCAGAUGUCUAUGUGUUUGUUUUAGAGCUAGAAAUAGCAA GUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUC GGUGCUsmUsmUsmU	450
gRNA2058	mUsmCsmCsCUCAGAUGUCUAUGUGUUUGUUUUAGAGCUAGAAAUAGCA AGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGU CGGUGCUsmUsmUsmU	451
gRNA2059	mAsmUsmCsCCUCAGAUGUCUAUGUGUUUGUUUUAGAGCUAGAAAUAGC AAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAG UCGGUGCUsmUsmUsmU	452
gRNA2060	mCsmUsmCsACCUCUGCAAGUAUUGGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGG UGCUsmUsmUsmU	453
gRNA1202	mUsmCsmUsCACCUCUGCAAGUAUUGGUUUUAGAGCUAGAAAUAGCAAG UUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCG GUGCUsmUsmUsmU	454
gRNA2062	mCsmUsmCsUCACCUCUGCAAGUAUUGGUUUUAGAGCUAGAAAUAGCAA GUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUC GGUGCUsmUsmUsmU	455
gRNA2063	mUsmCsmUsCUCACCUCUGCAAGUAUUGGUUUUAGAGCUAGAAAUAGCA AGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGU CGGUGCUsmUsmUsmU	456
gRNA2064	mUsmUsmCsUCUACCUCUGCAAGUAUUGGUUUUAGAGCUAGAAAUAGC AAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAG UCGGUGCUsmUsmUsmU	457
gRNA2065	mCsmUsmUsACAAUGACUGAGAUCUGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGG UGCUsmUsmUsmU	458
gRNA1204	mGsmCsmUsUACAAUGACUGAGAUCUGUUUUAGAGCUAGAAAUAGCAAG UUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCG GUGCUsmUsmUsmU	459
gRNA2067	mUsmGsmCsUUACAAUGACUGAGAUCUGUUUUAGAGCUAGAAAUAGCAA GUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUC GGUGCUsmUsmUsmU	460
gRNA2068	mGsmUsmGsCUUACAAUGACUGAGAUCUGUUUUAGAGCUAGAAAUAGCA AGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGU CGGUGCUsmUsmUsmU	461
gRNA2069	mUsmGsmUsGCUUACAAUGACUGAGAUCUGUUUUAGAGCUAGAAAUAGC AAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAG UCGGUGCUsmUsmUsmU	462
gRNA2070	mCsmUsmUsACAGUGACUGAGAUCUGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGG UGCUsmUsmUsmU	463
gRNA1999	mGsmCsmUsUACAGUGACUGAGAUCUGUUUUAGAGCUAGAAAUAGCAAG UUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCG GUGCUsmUsmUsmU	464
gRNA2072	mUsmGsmCsUUACAGUGACUGAGAUCUGUUUUAGAGCUAGAAAUAGCAA GUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUC GGUGCUsmUsmUsmU	465
gRNA2073	mGsmUsmGsCUUACAGUGACUGAGAUCUGUUUUAGAGCUAGAAAUAGCA AGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGU CGGUGCUsmUsmUsmU	466
gRNA2074	mUsmGsmUsGCUUACAGUGACUGAGAUCUGUUUUAGAGCUAGAAAUAGC AAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAG UCGGUGCUsmUsmUsmU	467

Table 1B: Representative sequences for guide polynucleotides for use in guiding a base editor to alter a complement factor B splice site or introduce a new stop codon into a complement factor B polynucleotide using base editing.²

Guide polynucleotide name	Guide polynucleotide sequence	SEQ ID NO
gRNA1181	mCsmUsmGsCAGGAUUGCACAACAUGGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	568
gRNA1182	mAsmUsmAsGGCCAUUUGUCUCCCCGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	569
gRNA1183	mCsmUsmCsUGCAGGUUGGUGUAAUCGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	570
gRNA1184	mAsmCsmGsCUCUCACCUGAUAGUCUGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	571
gRNA1185	mCsmUsmUsACAAUGACUGAGAUCUUGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	572
gRNA1186	mUsmCsmAsCCUCCGUUGUCACAGAUGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	573
gRNA1187	mUsmCsmGsCUUACCUCAGACAAGAGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	574
gRNA1188	mCsmAsmCsCCACAGGUGGCAAGUUAGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	575
gRNA1189	mAsmCsmAsGACCACAAGUUGAAGUCGUUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	576
gRNA1190	mUsmCsmUsGCAGGAUUGCACAACAUGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	577
gRNA1191	mGsmCsmAsGGAUUGCACAACAUGGGGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	578
gRNA1192	mCsmCsmCsUCAGAUGUCUAUGUGUUUGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	579
gRNA1193	mCsmCsmUsCAGAUGUCUAUGUGUUUGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	580
gRNA1194	mCsmUsmCsAGAUGUCUAUGUGUUUGGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	581
gRNA1195	mGsmUsmGsUCCCCAGCGCCCUUCAAGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	582

² “mN” indicates a 2'-OMe modification of the nucleotide “N”, and “Ns” indicates that the nucleotide “N” is linked to the following (i.e., 3') nucleotide by a phosphorothioate (PS).

Guide polynucleotide name	Guide polynucleotide sequence	SEQ ID NO
gRNA1196	mUsmGsmUsCCCCAGCGCCCUCAAAGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	583
gRNA1197	mCsmUsmAsCUUCAGGAGGGGAGAAGGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	584
gRNA1198	mUsmAsmCsUUCAGGAGGGGAGAAGCGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	585
gRNA1199	mCsmUsmCsCUUGCAGGUGAUUCUGGGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	586
gRNA1200	mUsmGsmCsAGGUUGGUGUAAUCAGCGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	587
gRNA1201	mGsmCsmAsGGUUGGUGUAAUCAGCUGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	588
gRNA1202	mUsmCsmUsCACCUCUGCAAGUAUUGGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	589
gRNA1203	mCsmUsmUsACUUUGUUGCUGGCAAGGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	590
gRNA1204	mGsmCsmUsUACAAUGACUGAGAUCUGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	591
gRNA1205	mUsmCsmAsCCCAGAUAAUCCUCCUGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	592
gRNA1206	mCsmCsmUsUCUGACCAUCAGUCAUGGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	593
gRNA1207	mCsmAsmAsAGGUCACCUUGGCAGGAGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	594
gRNA1208	mCsmUsmCsGCUUACCUCCAGACAAGGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	595
gRNA1209	mUsmCsmAsAAGCAAUCCACUGUCCAGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	596
gRNA1210	mCsmUsmCsCCAGACUCCUUAUGUAGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	597
gRNA1211	mCsmCsmCsAGGGGAACAACAGAAGCGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	598
gRNA1212	mAsmCsmAsGGUGGCAAGUUAUGGUGGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	599

Guide polynucleotide name	Guide polynucleotide sequence	SEQ ID NO
gRNA1213	mGsmCsmCsAGAUGAAAGCCAGUCUCGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	600
gRNA1214	mGsmUsmCsCCCAGCGCCCUCAAAGGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	601
gRNA1215	mUsmAsmCsAGAAAGGCAGCUGUGAGGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	602
gRNA1216	mGsmAsmGsGACUCACUUGAAUGAAAGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	603
gRNA1217	mUsmCsmUsCACCUIAUCCCCAUUCUGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	604
gRNA1218	mAsmUsmCsCUUACCUACGCUGACCUGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	605
gRNA1219	mUsmUsmAsCCUACGCUGACCUUGAUGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	606
gRNA1220	mCsmUsmCsCCUACCGAUCAUUUGGUGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	607
gRNA1221	mCsmUsmGsACCAUCAGUCAUGAGGAGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	608
gRNA1222	mCsmUsmUsCUCACCUCCGUUGUCACGUUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	609
gRNA1223	mUsmCsmCsCUCAGAUGUCUAUGUGUUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	610
gRNA1224	mCsmUsmGsCCAGAUGAAAGCCAGUCUGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	611
gRNA1225	mUsmUsmCsUCUCACCUCUGCAAGUAUGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	612
gRNA1226	mCsmCsmUsUACCUACGCUGACCUUGAGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	613
gRNA1227	mAsmCsmUsCACCAGAUAAUCCUCCGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	614
gRNA1228	mUsmCsmCsCUUCUGACCAUCAGUCAUGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	615
gRNA1229	mCsmUsmUsCAGGUGUGACCACACUCGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	616

Guide polynucleotide name	Guide polynucleotide sequence	SEQ ID NO
gRNA1230	mCsmCsmCsUCUCCACAGACCACAAGUGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	617
gRNA1231	mCsmUsmAsCAGAAAGGCAGCUGUGAGGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	618
gRNA1232	mGsmUsmAsUGUCUUACUUUGUUGCUGGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	619
gRNA1233	mUsmGsmUsCUUACUUUGUUGCUGGCAGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	620
gRNA1234	mUsmGsmCsAUCCUUACCUACGCUGACGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	621
gRNA1235	mGsmGsmAsUUCUGUGCUUACAAGACGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	622
gRNA1236	mCsmUsmUsGUAUCUCCUACCGAUCAGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	623
gRNA1237	mCsmUsmUsCUGACCAUCAGUCAUGAGGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	624
gRNA1238	mCsmCsmCsUAACCUCUGACCUUCAUAGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	625
gRNA1239	mAsmGsmGsAGGAUCCACCUUCUCAAGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	626
gRNA1240	mAsmUsmGsCUUCUCACCUCGUGUUGUCGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	627
gRNA1241	mUsmUsmCsUCCAAGAGGGCCAGGCACGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	628
gRNA1242	mAsmCsmCsAAAAGACUGUCAGGAAGGGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	629
gRNA1243	mAsmCsmCsUGCCAAGUGAAUGGCCGAGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	630
gRNA1244	mGsmAsmGsCAACAUGUGUCAAAGUCGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	631
gRNA1245	mUsmAsmCsACCAACCUGCAGAGGCAGGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	632
gRNA1246	mGsmGsmCsUUUCAUCUGGCAGAGAAGGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	633

Guide polynucleotide name	Guide polynucleotide sequence	SEQ ID NO
gRNA1247	mGsmAsmCsAUCUGAGGGAUAAAAAGGGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	634
gRNA1248	mUsmGsmUsUGUUCUUUUUGGGUGCCAGGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	635
gRNA1249	mAsmUsmCsGCACCGCCAAGUGAAUGGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	636
gRNA1250	mUsmGsmGsCCGAUGGAGUGGGCAGACGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	637
gRNA1251	mUsmCsmCsCAGCGGCGAACGUGUCAGGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	638
gRNA1252	mCsmCsmCsAGGGGAACAACAGAAGCGGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	639
gRNA1253	mGsmUsmCsACGAAGCAGCUCAAUGAAGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	640
gRNA1254	mGsmGsmCsCCUCCAGGCAGUACAGGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	641
gRNA1255	mUsmUsmUsCUACCAAUGAUCGGUAGGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	642
gRNA1256	mGsmCsmAsACCAUGGCAGGCCAAGAUGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	643
gRNA1257	mUsmCsmAsGCCAGGGCAGCACUUGAAGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	644
gRNA1258	mCsmUsmUsACUUUGUUGCUGGCAAGUGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	645
gRNA1259	mCsmUsmCsCCUCCUGAAGUAGGAGAGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	646
gRNA1260	mUsmUsmUsGAAGGGCGCUGGGGACACGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	647
gRNA1261	mUsmCsmUsUGGCCUGCCAUGGUUGCUGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	648
gRNA1262	mUsmGsmGsCCUGCCAUGGUUGCUUGUGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	649
gRNA1263	mAsmUsmGsAAGGAGUCUGGGAGAGUCGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	650

Guide polynucleotide name	Guide polynucleotide sequence	SEQ ID NO
gRNA1264	mGsmGsmAsGUCUGGGAGAGUCAGAAAGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	651
gRNA1265	mCsmGsmCsUGCAGAGGUAUGAGACAUGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	652
gRNA1266	mAsmCsmUsCCAUCGGCCAUCACUUGGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	653
gRNA1267	mGsmGsmGsGCCAGUAUUCGCCGUGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	654
gRNA1268	mGsmGsmAsUUGC UUUGAGAAGGGGGGGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	655
gRNA1269	mUsmUsmCsAGGGUGCUCCAGGACCCCGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	656
gRNA1270	mGsmCsmUsCCAGGACCCCGUAGAUCUGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	657
gRNA1271	mUsmGsmGsUCACACCUGAAGAGAAAGGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	658
gRNA1272	mCsmUsmUsACCUCCAGACAAGAGGCCGUGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	659
gRNA1356	mCsmUsmCsCUUCCGACUUCUCCAAGGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	660
gRNA1357	mUsmCsmCsUUCGACUUCUCCAAGGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	661
gRNA1358	mUsmCsmUsCCAAGAGGGCCAGGCACGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	662
gRNA1359	mCsmUsmCsAAGACCAAAAGACUGUCGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	663
gRNA1360	mAsmGsmAsCCAAAAGACUGUCAGGAGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	664
gRNA1361	mCsmCsmUsGCCAAGUGAAUGGCCGAGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	665
gRNA1362	mCsmUsmCsCCAGCGGCGAACGUGUCGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	666
gRNA1363	mCsmAsmGsCGGCGAACGUGUCAGGAGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	667

Guide polynucleotide name	Guide polynucleotide sequence	SEQ ID NO
gRNA1364	mCsmGsmGsCGAACGUGUCAGGAAGGGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	668
gRNA1365	mCsmGsmUsGUCAGGAAGGUGGCUCUGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	669
gRNA1366	mUsmUsmUsUCUACCAAUGAUCGGUGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	670
gRNA1367	mUsmUsmUsCUACCAAUGAUCGGUAGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	671
gRNA1368	mGsmCsmAsACAAAGUAAGACAUACUGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	672
gRNA1369	mAsmCsmCsUCUUUCAAGUGCUGCCCGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	673
gRNA1370	mGsmAsmAsACUCCAAGAUGAGGAUUGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	674
gRNA1371	mAsmAsmAsCUCCAAGAUGAGGAUUUGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	675
gRNA1372	mCsmAsmCsCAACCUGCAGAGGCAGUGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	676
gRNA1373	mAsmCsmCsAACCUGCAGAGGCAGUGGUUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	677
gRNA1374	mUsmGsmCsCUUUCUGUAGGGGAGGUGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	678
gRNA1375	mAsmAsmAsUGGGCCUAUAAAGGACAGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	679
gRNA1376	mCsmCsmCsUCCUGAAGUAGGAGAGUGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	680
gRNA1377	mUsmGsmGsCCUGCCAUGGUUGCUUGGUUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	681
gRNA1378	mUsmAsmGsACAUCUGAGGGAUAAAAGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	682
gRNA1379	mCsmAsmUsCUGAGGGAUAAAAGGAGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	683
gRNA1380	mUsmGsmCsAAUCCUGCAGAAGAGACGUUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	684

Guide polynucleotide name	Guide polynucleotide sequence	SEQ ID NO
gRNA1381	mGsmUsmGsCGGUUCCAGCCUUCAGGGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	685
gRNA1382	mUsmGsmCsGGUUCCAGCCUUCAGGAGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	686
gRNA1383	mGsmAsmCsCCAAAUUUUGGGGUAUGGUUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	687
gRNA1384	mCsmAsmCsUCCAUCGGCCAUUCACUGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	688
gRNA1385	mGsmUsmGsGAUUGCUUUGAGAAGGGGUUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	689
gRNA1386	mCsmCsmCsCAGGGAUCCUGCUCUCUGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	690
gRNA1387	mUsmCsmAsAGACCAAAGACUGUCAGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	691
gRNA1388	mGsmCsmAsCCUGCCAAGUGAAUGGCGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	692
gRNA1389	mCsmUsmGsCCAAGUGAAUGGCCGAUGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	693
gRNA1390	mGsmAsmAsUGGCCGAUGGAGUGGGCGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	694
gRNA1391	mAsmGsmUsGGGCAGACAGCGAUCUGGUUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	695
gRNA1392	mGsmGsmCsAGCCAGUACCGCCUUGAGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	696
gRNA1393	mUsmCsmCsCAGCGGCGAACGUGUCAGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	697
gRNA1394	mGsmUsmGsUCAGGAAGGUGGCUCUUGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	698
gRNA1395	mAsmGsmGsGGAACAACAGAAGCGGAGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	699
gRNA1396	mCsmCsmUsCCAGGCAGUGUACAGCAGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	700
gRNA1397	mUsmUsmCsUACCAAUGAUCGGUAGGUUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	701

Guide polynucleotide name	Guide polynucleotide sequence	SEQ ID NO
gRNA1398	mCsmUsmAsCCAAUGAUCGGUAGGGGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	702
gRNA1399	mCsmAsmAsGCAACCAUGGCAGGCCAGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	703
gRNA1400	mUsmAsmUsGGCCAGACUAUCAGGUGGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	704
gRNA1401	mCsmAsmCsUUGCCAGCAACAAAGUAGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	705
gRNA1402	mGsmCsmUsCAAUAUGCCCCAGGCUAGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	706
gRNA1403	mCsmUsmUsUCAAGUGCUGCCUGGCGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	707
gRNA1404	mCsmCsmUsUCAGCCAGGGCAGCACUGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	708
gRNA1405	mCsmAsmGsCCAGGGCAGCACUUGAAGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	709
gRNA1406	mGsmCsmCsUUUCUGUAGGGGAGGUGGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	710
gRNA1407	mAsmAsmUsGGGCCUAUAAAGGACAAGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	711
gRNA1408	mUsmGsmGsGCCUAUAAAGGACAAGGGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	712
gRNA1409	mGsmUsmGsUCCCCAAACCAUGCCACGUUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	713
gRNA1410	mGsmUsmUsCCCAAACCAUGCCACAGGUUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	714
gRNA1411	mGsmCsmGsGUUCCAGCCUUCAGGAGGUUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	715
gRNA1412	mUsmUsmGsUGGUCUGUGGAGAGGGAGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	716
gRNA1413	mGsmAsmGsUCUGGGAGAGUCAGAAAGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	717
gRNA1414	mCsmGsmCsUCCAAGAGCCACCUUCCGUUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	718

Guide polynucleotide name	Guide polynucleotide sequence	SEQ ID NO
gRNA1415	mUsmAsmCsCCCGCUGCAGAGGUAUGGUUUUAGAGCUAGAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	719
gRNA1416	mGsmGsmGsCCAGUAUCCCCGUUCUGUUUUAGAGCUAGAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	720
gRNA1417	mUsmGsmGsAUUGC UUUGAGAAGGGGGUUUUAGAGCUAGAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	721
gRNA1418	mAsmGsmGsGUGCUCCAGGACCCGUGUUUUAGAGCUAGAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	722
gRNA1419	mCsmAsmCsCUGAAGAGAAAGGCUGAGUUUUAGAGCUAGAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCUsmUsmUsmU	723

Table 1C: Representative sequences for guide polynucleotides for use in guiding a base editor to alter a complement factor B splice site or introduce a new stop codon into a complement factor B polynucleotide using base editing.³

Guide polynucleotide name	Guide polynucleotide sequence	SEQ ID NO
GuideDesign10_CBE_NGA_2 Ont_4-9_006_- 31947177 spCas9	mCsmUsmUsCUCACCUCGUGUCACGUUUUAGAGCUAGA AAUAGCAAGUUAUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	724
GuideDesign10_CBE_NGA_2 Ont_4-9_006_- 31948943 spCas9	mCsmUsmGsACCAUCAGUCAUGAGGAGUUUUAGAGCUAGA AAUAGCAAGUUAUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	725
GuideDesign10_CBE_NGA_2 Ont_4-9_006_- 31949542 spCas9	mCsmUsmCsCCUACCGAUCAUUUGGUGUUUUAGAGCUAGA AAUAGCAAGUUAUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	726
GuideDesign10_CBE_NGA_2 Ont_4-9_006_- 31950384 spCas9	mUsmUsmAsCCUACGCUGACCUUGAUGUUUUAGAGCUAGA AAUAGCAAGUUAUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	727
GuideDesign10_CBE_NGA_2 Ont_4-9_006_- 31950388 spCas9	mAsmUsmCsCUUACCUACGCUGACCUUUUUAGAGCUAGA AAUAGCAAGUUAUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	728
GuideDesign10_CBE_NGA_2 Ont_4-9_006_- 31951227 spCas9	mUsmCsmUsCACCUUAUCCCCAUUCUGUUUUAGAGCUAGA AAUAGCAAGUUAUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	729
GuideDesign10_CBE_NGC_2 Ont_4-9_009_- 31946270 spCas9	mUsmCsmGsCUUACCUCCAGACAAGAGUUUUAGAGCUAGA AAUAGCAAGUUAUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	730
GuideDesign10_CBE_NGC_2 Ont_4-9_009_- 31947173 spCas9	mUsmCsmAsCCUCCGUGUCACAGAUUUUUAGAGCUAGA AAUAGCAAGUUAUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	731

³ “mN” indicates a 2'-OMe modification of the nucleotide “N”, and “Ns” indicates that the nucleotide “N” is linked to the following (i.e., 3') nucleotide by a phosphorothioate (PS).

GuideDesign10_CBE_NGC_2 0nt_4-9_009_- 31950129 spCas9	mCsmUsmUsACAAUGACUGAGAUCUUGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	732
GuideDesign10_CBE_NGC_2 0nt_4-9_009_- 31951854 spCas9	mAsmAsmCsCUGCAGAGGCAGUGGGGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	733
GuideDesign10_CBE_NGG_2 0nt_4-9_003_- 31946271 spCas9	mCsmUsmCsGCUUACCUCAGACAAGGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	734
GuideDesign10_CBE_NGG_2 0nt_4-9_003_- 31948947 spCas9	mCsmCsmUsUCUGACCAUCAGUCAUGGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	735
GuideDesign10_CBE_NGG_2 0nt_4-9_003_- 31949325 spCas9	mUsmCsmAsCCCAGAUAAUCCUCCUGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	736
GuideDesign10_CBE_NGG_2 0nt_4-9_003_- 31950130 spCas9	mGsmCsmUsUACAAUGACUGAGAUCUGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	737
GuideDesign10_CBE_NGG_2 0nt_4-9_003_- 31950926 spCas9	mCsmUsmUsACUUUGUUGCUGGCAAGGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	738
GuideDesign10_CBE_NGG_2 0nt_4-9_003_- 31951456 spCas9	mUsmCsmUsCACCUCUGCAAGUAUUGGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	739
GuideDesign3_ABE_NGA_20 nt_3-12_019_- 31946273 spCas9	mCsmCsmCsUCGCUUACCUCAGACAGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	740
GuideDesign3_ABE_NGA_20 nt_3-12_019_- 31947177 spCas9	mCsmUsmUsCUCACCUCGUGUCACGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	741
GuideDesign3_ABE_NGA_20 nt_3-12_019_- 31947511 spCas9	mGsmGsmUsCAAAGGUCACCUUGGCAGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	742
GuideDesign3_ABE_NGA_20 nt_3-12_019_- 31948064 spCas9	mUsmUsmCsCACCUCUCAAUUAAGUGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	743
GuideDesign3_ABE_NGA_20 nt_3-12_019_- 31948500 spCas9	mUsmAsmAsCCUCUGACCUUCAUAUUGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	744
GuideDesign3_ABE_NGA_20 nt_3-12_019_- 31948943 spCas9	mCsmUsmGsACCAUCAGUCAUGAGGAGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	745
GuideDesign3_ABE_NGA_20 nt_3-12_019_- 31948946 spCas9	mCsmUsmUsCUGACCAUCAGUCAUGAGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	746
GuideDesign3_ABE_NGA_20 nt_3-12_019_- 31948949 spCas9	mUsmCsmCsCUUCUGACCAUCAGUCAGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	747
GuideDesign3_ABE_NGA_20 nt_3-12_019_- 31949542 spCas9	mCsmUsmCsCCUACCGAUCAUUUGGUGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	748
GuideDesign3_ABE_NGA_20 nt_3-12_019_- 31950136 spCas9	mUsmUsmCsUGUGCUUACAAUGACUGGUUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	749

GuideDesign3_ABE_NGA_20 nt_3-12_019_- 31950384_spCas9	mUsmUsmAsCCUACGCUGACCUUGAUGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	750
GuideDesign3_ABE_NGA_20 nt_3-12_019_- 31950388_spCas9	mAsmUsmCsCUUACCUACGCUGACCUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	751
GuideDesign3_ABE_NGA_20 nt_3-12_019_- 31951227_spCas9	mUsmCsmUsCACCUUAUCCCCAUUCUGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	752
GuideDesign3_ABE_NGA_20 nt_3-12_019_- 31951591_spCas9	mGsmAsmGsGACUCACUUGAAUGAAAGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	753
GuideDesign3_ABE_NGA_20 nt_3- 12_019_+31947000_spCas9	mUsmCsmAsAAGCAAUCCACUGUCCAGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	754
GuideDesign3_ABE_NGA_20 nt_3- 12_019_+31947734_spCas9	mCsmUsmCsCCAGACUCCUUAUGUAGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	755
GuideDesign3_ABE_NGA_20 nt_3- 12_019_+31947933_spCas9	mCsmUsmGsGCACCCAGGGGAACAACGUUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	756
GuideDesign3_ABE_NGA_20 nt_3- 12_019_+31947939_spCas9	mCsmCsmCsAGGGGAACAACAGAAGCGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	757
GuideDesign3_ABE_NGA_20 nt_3- 12_019_+31948369_spCas9	mAsmCsmAsGGUGGCAAGUUAUGGUGGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	758
GuideDesign3_ABE_NGA_20 nt_3- 12_019_+31948818_spCas9	mCsmCsmUsCUCCACAGACCACAAGUGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	759
GuideDesign3_ABE_NGA_20 nt_3- 12_019_+31950044_spCas9	mGsmCsmCsAGAUGAAAGCCAGUCUCGUUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	760
GuideDesign3_ABE_NGA_20 nt_3- 12_019_+31950277_spCas9	mGsmUsmCsCCCAGCGCCCUCAAAGGUUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	761
GuideDesign3_ABE_NGA_20 nt_3- 12_019_+31950611_spCas9	mAsmCsmUsUCAGGAGGGGAGAAGCGGUUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	762
GuideDesign3_ABE_NGA_20 nt_3- 12_019_+31951331_spCas9	mCsmCsmCsCUACAGAAAGGCAGCUGGUUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	763
GuideDesign3_ABE_NGA_20 nt_3- 12_019_+31951333_spCas9	mCsmCsmUsACAGAAAGGCAGCUGUGGUUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	764
GuideDesign3_ABE_NGA_20 nt_3- 12_019_+31951335_spCas9	mUsmAsmCsAGAAAGGCAGCUGAGGUUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	765
GuideDesign3_ABE_NGA_20 nt_3-9_005_- 31948064_spCas9	mUsmUsmCsCACCUUCUCAAUUAAGUGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	766
GuideDesign3_ABE_NGA_20 nt_3-9_005_- 31948946_spCas9	mCsmUsmUsCUGACCAUCAGUCAUGAGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	767

GuideDesign3_ABE_NGA_20 nt_3- 9_005 + 31950611 spCas9	mAsmCsmUsUCAGGAGGGGAGAAGCGGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	768
GuideDesign3_ABE_NGA_20 nt_3- 9_005 + 31951331 spCas9	mCsmCsmCsCUACAGAAAGGCAGCUGGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	769
GuideDesign3_ABE_NGA_20 nt_3- 9_005 + 31951333 spCas9	mCsmCsmUsACAGAAAGGCAGCUGGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	770
GuideDesign3_ABE_NGC_20 nt_3-12_020 - 31946270 spCas9	mUsmCsmGsCUUACCUCAGACAAGAGUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	771
GuideDesign3_ABE_NGC_20 nt_3-12_020 - 31946593 spCas9	mGsmCsmCsCUCAAACCUCUGCACUCGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	772
GuideDesign3_ABE_NGC_20 nt_3-12_020 - 31947173 spCas9	mUsmCsmAsCCUCCGUUGUCACAGAUGUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	773
GuideDesign3_ABE_NGC_20 nt_3-12_020 - 31947507 spCas9	mAsmAsmAsGGUCACCUUGGCAGGAAGUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	774
GuideDesign3_ABE_NGC_20 nt_3-12_020 - 31947832 spCas9	mCsmUsmGsUCUUCAAACCUGGGCCGGUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	775
GuideDesign3_ABE_NGC_20 nt_3-12_020 - 31950129 spCas9	mCsmUsmUsACAAUGACUGAGAUCUUGUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	776
GuideDesign3_ABE_NGC_20 nt_3-12_020 - 31950759 spCas9	mAsmCsmGsCUCUCACCUGAUAGUCUGUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	777
GuideDesign3_ABE_NGC_20 nt_3-12_020 - 31950932 spCas9	mGsmUsmAsUGUCUUACUUUGUUGCUGUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	778
GuideDesign3_ABE_NGC_20 nt_3- 12_020 + 31947335 spCas9	mAsmUsmAsCCUCUGCAGCGGGGUACGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	779
GuideDesign3_ABE_NGC_20 nt_3- 12_020 + 31947936 spCas9	mGsmCsmAsCCCAGGGGAACAACAGAGUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	780
GuideDesign3_ABE_NGC_20 nt_3- 12_020 + 31949236 spCas9	mCsmUsmGsCAGGAUUGCACAACAUGGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	781
GuideDesign3_ABE_NGC_20 nt_3- 12_020 + 31950607 spCas9	mUsmCsmCsUACUUCAGGAGGGGAGAGUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	782
GuideDesign3_ABE_NGC_20 nt_3- 12_020 + 31950863 spCas9	mAsmUsmAsGGCCCCAUUUGUCUCCCCGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	783
GuideDesign3_ABE_NGC_20 nt_3- 12_020 + 31951132 spCas9	mUsmAsmUsUCGUCCAGAGGAAGAGCGUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	784
GuideDesign3_ABE_NGC_20 nt_3- 12_020 + 31951139 spCas9	mCsmCsmAsGAGGAAGAGCUGCUCCCCGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	785

GuideDesign3_ABE_NGC_20 nt_3- 12_020 + 31951542_spCas9	mCsmUsmCsUCCUUGCAGGUGAUUCUGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	786
GuideDesign3_ABE_NGC_20 nt_3- 12_020 + 31951545_spCas9	mUsmCsmCsUUGCAGGUGAUUCUGGCGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	787
GuideDesign3_ABE_NGC_20 nt_3- 12_020 + 31951866_spCas9	mCsmUsmCsUGCAGGUUGGUGUAUUCGUUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	788
GuideDesign3_ABE_NGC_20 nt_3-9_008_- 31946593_spCas9	mGsmCsmCsCUCAAACCUCUGCACUCGUUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	789
GuideDesign3_ABE_NGC_20 nt_3-9_008_- 31947507_spCas9	mAsmAsmAsGGUCACCUUGGCAGGAAGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	790
GuideDesign3_ABE_NGC_20 nt_3- 9_008 + 31947936_spCas9	mGsmCsmAsCCCAGGGGAACAACAGAGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	791
GuideDesign3_ABE_NGC_20 nt_3- 9_008 + 31951139_spCas9	mCsmCsmAsGAGGAAGAGCUGCUCGCCGUUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	792
GuideDesign3_ABE_NGC_20 nt_3- 9_008 + 31951545_spCas9	mUsmCsmCsUUGCAGGUGAUUCUGGCGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	793
GuideDesign3_ABE_NGG_20 nt_3-12_018_- 31946271_spCas9	mCsmUsmCsGCUUACCUCAGACAAGGUUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	794
GuideDesign3_ABE_NGG_20 nt_3-12_018_- 31947508_spCas9	mCsmAsmAsAGGUCACCUUGGCAGGAGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	795
GuideDesign3_ABE_NGG_20 nt_3-12_018_- 31948947_spCas9	mCsmCsmUsCCUGACCAUCAGUCAUGGUUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	796
GuideDesign3_ABE_NGG_20 nt_3-12_018_- 31949325_spCas9	mUsmCsmAsCCCAGAUAAUCCUCCCUGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	797
GuideDesign3_ABE_NGG_20 nt_3-12_018_- 31949546_spCas9	mGsmUsmAsUCUCCCUACCGAUCAUUGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	798
GuideDesign3_ABE_NGG_20 nt_3-12_018_- 31950130_spCas9	mGsmCsmUsUACAAUGACUGAGAUCUGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	799
GuideDesign3_ABE_NGG_20 nt_3-12_018_- 31950760_spCas9	mGsmAsmCsGCUCUCACCUGAUAGUCGUUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	800
GuideDesign3_ABE_NGG_20 nt_3-12_018_- 31950926_spCas9	mCsmUsmUsACUUUGUUGCUGGCAAGGUUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	801
GuideDesign3_ABE_NGG_20 nt_3-12_018_- 31950933_spCas9	mAsmGsmUsAUGUCUUACUUUGUUGCGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	802
GuideDesign3_ABE_NGG_20 nt_3-12_018_- 31951456_spCas9	mUsmCsmUsCACCUCUGCAAGUAUUGGUUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	803

GuideDesign3_ABE_NGG_20 nt_3-12_018_- 31951457_spCas9	mCsmUsmCsUCACCUCUGCAAGUAUUGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	804
GuideDesign3_ABE_NGG_20 nt_3-12_018_- 31951458_spCas9	mUsmCsmUsCUCACCUCUGCAAGUAUGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	805
GuideDesign3_ABE_NGG_20 nt_3- 12_018_+31947938_spCas9	mAsmCsmCsCAGGGGAACAACAGAAGGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	806
GuideDesign3_ABE_NGG_20 nt_3- 12_018_+31948364_spCas9	mCsmAsmCsCCACAGGUGGCAAGUUAGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	807
GuideDesign3_ABE_NGG_20 nt_3- 12_018_+31948825_spCas9	mAsmCsmAsGACCACAAGUUGAAGUCGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	808
GuideDesign3_ABE_NGG_20 nt_3- 12_018_+31949234_spCas9	mUsmUsmCsUGCAGGAUUGCACAACAGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	809
GuideDesign3_ABE_NGG_20 nt_3- 12_018_+31949235_spCas9	mUsmCsmUsGCAGGAUUGCACAACAGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	810
GuideDesign3_ABE_NGG_20 nt_3- 12_018_+31949238_spCas9	mGsmCsmAsGGAUUGCACAACAUGGGGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	811
GuideDesign3_ABE_NGG_20 nt_3- 12_018_+31949412_spCas9	mCsmCsmCsUCAGAUGUCUAUGUGUUGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	812
GuideDesign3_ABE_NGG_20 nt_3- 12_018_+31949413_spCas9	mCsmCsmUsCAGAUGUCUAUGUGUUUGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	813
GuideDesign3_ABE_NGG_20 nt_3- 12_018_+31949414_spCas9	mCsmUsmCsAGAUGUCUAUGUGUUUGGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	814
GuideDesign3_ABE_NGG_20 nt_3- 12_018_+31950275_spCas9	mGsmUsmGsUCCCCAGCGCCCUUCAAGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	815
GuideDesign3_ABE_NGG_20 nt_3- 12_018_+31950276_spCas9	mUsmGsmUsCCCCAGCGCCCUUCAAGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	816
GuideDesign3_ABE_NGG_20 nt_3- 12_018_+31950609_spCas9	mCsmUsmAsCUUCAGGAGGGGAGAAGGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	817
GuideDesign3_ABE_NGG_20 nt_3- 12_018_+31950610_spCas9	mUsmAsmCsUUCAGGAGGGGAGAAGCGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	818
GuideDesign3_ABE_NGG_20 nt_3- 12_018_+31951541_spCas9	mCsmCsmUsCUCCUUGCAGGUGAUUCGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	819
GuideDesign3_ABE_NGG_20 nt_3- 12_018_+31951544_spCas9	mCsmUsmCsCUUGCAGGUGAUUCUGGGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	820
GuideDesign3_ABE_NGG_20 nt_3- 12_018_+31951869_spCas9	mUsmGsmCsAGGUUGGUGUAAUCAGCGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	821

GuideDesign3_ABE_NGG_20 nt_3- 12_018 + 31951870_spCas9	mGsmCsmAsGGUUGGUGUAAUCAGCUGUUUUAGAGCUAGA AAUAGCAAGUUAUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	822
GuideDesign3_ABE_NGG_20 nt_3-9_002_- 31951457_spCas9	mCsmUsmCsUCACCUCUGCAAGUAUUGUUUUAGAGCUAGA AAUAGCAAGUUAUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	823
GuideDesign3_ABE_NGG_20 nt_3-9_002_- 31951458_spCas9	mUsmCsmUsCUCACCUCUGCAAGUAUGUUUUAGAGCUAGA AAUAGCAAGUUAUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	824
GuideDesign3_ABE_NGG_20 nt_3- 9_002 + 31947938_spCas9	mAsmCsmCsCAGGGGAACAACAGAAGGUUUUAGAGCUAGA AAUAGCAAGUUAUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	825
GuideDesign3_ABE_NGG_20 nt_3- 9_002 + 31949234_spCas9	mUsmUsmCsUGCAGGAUUGCACAACAGUUUUAGAGCUAGA AAUAGCAAGUUAUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	826
GuideDesign3_ABE_NNNRR T_21nt_5-14_014_- 31948945_saCas9	mUsmCsmCsCUUCUGACCAUCAGUCAUGUUUUAGUACUCU GUAAUGAAAAUUAACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsm U	827
GuideDesign3_ABE_NNNRR T_21nt_5-14_014_- 31949323_saCas9	mAsmCsmUsCACCCAGAUAAUCCUCCCGUUUUAGUACUCU GUAAUGAAAAUUAACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsm U	828
GuideDesign3_ABE_NNNRR T_21nt_5-14_014_- 31950382_saCas9	mCsmCsmUsUACCUACGCUGACCUUGAGUUUUAGUACUCU GUAAUGAAAAUUAACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsm U	829
GuideDesign3_ABE_NNNRR T_21nt_5-14_014_- 31951226_saCas9	mGsmUsmUsUCUCACCUUAUCCCCAUUGUUUUAGUACUCU GUAAUGAAAAUUAACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsm U	830
GuideDesign3_ABE_NNNRR T_21nt_5-14_014_- 31951455_saCas9	mUsmUsmCsUCUCACCUCUGCAAGUAUGUUUUAGUACUCU GUAAUGAAAAUUAACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsm U	831
GuideDesign3_ABE_NNNRR T_21nt_5- 14_014_+ 31948361_saCas9	mCsmCsmUsCACCCACAGGUGGCAAGUGUUUUAGUACUCU GUAAUGAAAAUUAACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsm U	832
GuideDesign3_ABE_NNNRR T_21nt_5- 14_014_+ 31949411_saCas9	mUsmCsmCsCUCAGAUGUCUAUGUGUUGUUUUAGUACUCU GUAAUGAAAAUUAACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsm U	833
GuideDesign3_ABE_NNNRR T_21nt_5- 14_014_+ 31950034_saCas9	mCsmUsmCsCUUCUCUGCCAGAUGAAAGUUUUAGUACUCU GUAAUGAAAAUUAACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsm U	834
GuideDesign3_ABE_NNNRR T_21nt_5- 14_014_+ 31950042_saCas9	mCsmUsmGsCCAGAUGAAAGCCAGUCUGUUUUAGUACUCU GUAAUGAAAAUUAACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsm U	835
GuideDesign3_ABE_VTTN_2 2nt_5-9_017_- 31946593_cas12b	mGsmUsmUsCUGUCUUUUUGGUCAGGACAACCGUCUAGCUA UAAGUCUGCAGGGUGUGAGAAACUCCUAUUGCUGGACGA UGUCUCUUACGAGGCAUAGCACCCCUCAAACCUCUGCAC UCsmUsmGsmC	836

GuideDesign3_ABE_VTTN_2 2nt_5-9_017_- _31950134_cas12b	mGsmUsmUsCUGUCUUUUGGUCAGGACAACCGUCUAGCUA UAAGUGCUGCAGGGUGUGAGAAACUCCUAUUGCUGGACGA UGUCUCUUACGAGGCAUAGCACUGUGCUUACAAUGACUG AGsmAsmUsmC	837
GuideDesign3_ABE_VTTN_2 2nt_5-9_017_- _31950390_cas12b	mGsmUsmUsCUGUCUUUUGGUCAGGACAACCGUCUAGCUA UAAGUGCUGCAGGGUGUGAGAAACUCCUAUUGCUGGACGA UGUCUCUUACGAGGCAUAGCACCAUCCUUAACUACGCUG ACsmCsmUsmU	838
GuideDesign3_ABE_VTTN_2 2nt_5-9_017_- _31951457_cas12b	mGsmUsmUsCUGUCUUUUGGUCAGGACAACCGUCUAGCUA UAAGUGCUGCAGGGUGUGAGAAACUCCUAUUGCUGGACGA UGUCUCUUACGAGGCAUAGCACUCUCACCUCUGCAAGUA UUsmGsmGsmG	839
GuideDesign3_ABE_VTTN_2 2nt_5- 9_017_+_31946360_cas12b	mGsmUsmUsCUGUCUUUUGGUCAGGACAACCGUCUAGCUA UAAGUGCUGCAGGGUGUGAGAAACUCCUAUUGCUGGACGA UGUCUCUUACGAGGCAUAGCACCUUCUUCAGGUGUGACCA CCsmAsmCsmU	840
GuideDesign3_ABE_VTTN_2 2nt_5- 9_017_+_31946996_cas12b	mGsmUsmUsCUGUCUUUUGGUCAGGACAACCGUCUAGCUA UAAGUGCUGCAGGGUGUGAGAAACUCCUAUUGCUGGACGA UGUCUCUUACGAGGCAUAGCACUCAAGCAAUCCACUGU CCsmAsmAsmG	841
GuideDesign3_ABE_VTTN_2 2nt_5- 9_017_+_31950037_cas12b	mGsmUsmUsCUGUCUUUUGGUCAGGACAACCGUCUAGCUA UAAGUGCUGCAGGGUGUGAGAAACUCCUAUUGCUGGACGA UGUCUCUUACGAGGCAUAGCACUCUGCCAGAUGAAAGCC AGsmUsmCsmU	842
GuideDesign3_ABE_VTTN_2 2nt_5- 9_017_+_31950272_cas12b	mGsmUsmUsCUGUCUUUUGGUCAGGACAACCGUCUAGCUA UAAGUGCUGCAGGGUGUGAGAAACUCCUAUUGCUGGACGA UGUCUCUUACGAGGCAUAGCACUGUCCCCAGCGCCCUUC AAsmAsmGsmG	843
GuideDesign3_ABE_VTTN_2 2nt_5- 9_017_+_31950853_cas12b	mGsmUsmUsCUGUCUUUUGGUCAGGACAACCGUCUAGCUA UAAGUGCUGCAGGGUGUGAGAAACUCCUAUUGCUGGACGA UGUCUCUUACGAGGCAUAGCACUCCUUUAUAGGCCCAUU UGsmUsmCsmU	844
GuideDesign3_ABE_VTTN_2 2nt_5- 9_017_+_31951133_cas12b	mGsmUsmUsCUGUCUUUUGGUCAGGACAACCGUCUAGCUA UAAGUGCUGCAGGGUGUGAGAAACUCCUAUUGCUGGACGA UGUCUCUUACGAGGCAUAGCACGUCCAGAGGAAGAGCUG CUsmCsmCsmC	845
GuideDesign3_CBE_NNGRR T_21nt_3-12_012_- _31948945_saCas9	mUsmCsmCsCUUCUGACCAUCAGUCAUGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGC AAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsm U	846
GuideDesign3_CBE_NNGRR T_21nt_3-12_012_- _31949323_saCas9	mAsmCsmUsCACCCAGAUAAUCCUCCCGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGC AAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsm U	847
GuideDesign3_CBE_NNGRR T_21nt_3-12_012_- _31950382_saCas9	mCsmCsmUsUACCUACGCUGACCUUGAGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGC AAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsm U	848
GuideDesign3_CBE_NNGRR T_21nt_3-12_012_- _31951455_saCas9	mUsmUsmCsUCUCACCUCUGCAAGUAUGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGC AAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsm U	849
GuideDesign3_CBE_NNNRR T_21nt_3-12_015_- _31947176_saCas9	mAsmUsmGsCUUCUCACCUCCGUUGUCGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGC AAAAUG	850

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GuideDesign3_CBE_NNNRR T_21nt_3-12_015_- _31947927_saCas9	mUsmGsmUsUGUUCUUUUUGGUGCCAGGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	851
GuideDesign3_CBE_NNNRR T_21nt_3-12_015_- _31948942_saCas9	mCsmUsmUsCUGACCAUCAGUCAUGAGGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	852
GuideDesign3_CBE_NNNRR T_21nt_3-12_015_- _31948945_saCas9	mUsmCsmCsCUUCUGACCAUCAGUCAUGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	853
GuideDesign3_CBE_NNNRR T_21nt_3-12_015_- _31949323_saCas9	mAsmCsmUsCACCAGAUAAUCCUCCGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	854
GuideDesign3_CBE_NNNRR T_21nt_3-12_015_- _31949397_saCas9	mGsmAsmCsAUCUGAGGGAUAAAAGGGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	855
GuideDesign3_CBE_NNNRR T_21nt_3-12_015_- _31950031_saCas9	mGsmGsmCsUUUCAUCUGGCAGAGAAGGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	856
GuideDesign3_CBE_NNNRR T_21nt_3-12_015_- _31950382_saCas9	mCsmCsmUsUACCUACGCUGACCUUGAGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	857
GuideDesign3_CBE_NNNRR T_21nt_3-12_015_- _31950387_saCas9	mUsmGsmCsAUCCUUACCUACGCUGACGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	858
GuideDesign3_CBE_NNNRR T_21nt_3-12_015_- _31950925_saCas9	mUsmGsmUsCUUACUUUGUUGCUGGCAGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	859
GuideDesign3_CBE_NNNRR T_21nt_3-12_015_- _31950928_saCas9	mGsmUsmAsUGUCUUACUUUGUUGCUGGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	860
GuideDesign3_CBE_NNNRR T_21nt_3-12_015_- _31951226_saCas9	mGsmUsmUsUCUCACCUUAUCCCCAUUGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	861
GuideDesign3_CBE_NNNRR T_21nt_3-12_015_- _31951455_saCas9	mUsmUsmCsUCUCACCUCUGCAAGUAUGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	862
GuideDesign3_CBE_NNNRR T_21nt_3-12_015_- _31951856_saCas9	mUsmAsmCsACCAACCUGCAGAGGCAGGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	863

GuideDesign10_CBE_NGA_2 Ont 4-9_006_- 31946352 spCas9	mCsmAsmCsCUGAAGAGAAAGGCUGAGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	864
GuideDesign10_CBE_NGA_2 Ont 4-9_006_- 31946990 spCas9	mUsmGsmGsAUUGCUUUGAGAAGGGGGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	865
GuideDesign10_CBE_NGA_2 Ont 4-9_006_- 31947331 spCas9	mUsmAsmCsCCCCGUGCAGAGGUAUGGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	866
GuideDesign10_CBE_NGA_2 Ont 4-9_006_- 31947722 spCas9	mGsmAsmGsUCUGGGAGAGUCAGAAAGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	867
GuideDesign10_CBE_NGA_2 Ont 4-9_006_- 31950849 spCas9	mUsmGsmGsGCCUAUAAAGGACAAGGGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	868
GuideDesign10_CBE_NGA_2 Ont 4-9_006_- 31950851 spCas9	mAsmAsmUsGGGCCUAUAAAGGACAAGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	869
GuideDesign10_CBE_NGA_2 Ont 4-9_006_- 31951323 spCas9	mGsmCsmCsUUUCUGUAGGGGAGGUGGUUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	870
GuideDesign10_CBE_NGG_2 Ont 4-9_003_- 31946991 spCas9	mGsmUsmGsGAUUGCUUUGAGAAGGGGGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	871
GuideDesign10_CBE_NGG_2 Ont 4-9_003_- 31949226 spCas9	mUsmGsmCsAAUCCUGCAGAAGAGACGUUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	872
GuideDesign10_CBE_NGG_2 Ont 4-9_003_- 31949399 spCas9	mCsmAsmUsCUGAGGGGAUAAAAGGAGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	873
GuideDesign10_CBE_NGG_2 Ont 4-9_003_- 31949403 spCas9	mUsmAsmGsACAUCUGAGGGGAUAAAAGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	874
GuideDesign10_CBE_NGG_2 Ont 4-9_003_- 31950600 spCas9	mCsmCsmCsUCCUGAAGUAGGAGAGUGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	875
GuideDesign10_CBE_NGG_2 Ont 4-9_003_- 31950852 spCas9	mAsmAsmAsUGGGCCUAUAAAGGACAGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	876
GuideDesign10_CBE_NGG_2 Ont 4-9_003_- 31951324 spCas9	mUsmGsmCsCUUUCUGUAGGGGAGGUGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	877
GuideDesign10_CBE_NGG_2 Ont 4-9_003_- 31951857 spCas9	mAsmCsmCsAACCUGCAGAGGCAGUGGUUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	878
GuideDesign3_ABE_NGA_20 nt 3-9_005_- 31947177 spCas9	mCsmUsmUsCUCACCUCGUGUCACGUUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	879
GuideDesign3_ABE_NGA_20 nt 3-9_005_- 31947177 spCas9	mCsmUsmUsCUCACCUCGUGUCACGUUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	880
GuideDesign3_ABE_NGA_20 nt 3-9_005_- 31948943 spCas9	mCsmUsmGsACCAUCAGUCAUGAGGAGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	881

GuideDesign3_ABE_NGA_20 nt_3-9_005_- 31948943_spCas9	mCsmUsmGsACCAUCAGUCAUGAGGAGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	882
GuideDesign3_ABE_NGA_20 nt_3-9_005_- 31949542_spCas9	mCsmUsmCsCCUACCGAUCAUUUGGUGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	883
GuideDesign3_ABE_NGA_20 nt_3-9_005_- 31949542_spCas9	mCsmUsmCsCCUACCGAUCAUUUGGUGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	884
GuideDesign3_ABE_NGA_20 nt_3-9_005_- 31950384_spCas9	mUsmUsmAsCCUACGCUGACCUUGAUGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	885
GuideDesign3_ABE_NGA_20 nt_3-9_005_- 31950384_spCas9	mUsmUsmAsCCUACGCUGACCUUGAUGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	886
GuideDesign3_ABE_NGA_20 nt_3-9_005_- 31950388_spCas9	mAsmUsmCsCUUACCUACGCUGACCUUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	887
GuideDesign3_ABE_NGA_20 nt_3-9_005_- 31950388_spCas9	mAsmUsmCsCUUACCUACGCUGACCUUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	888
GuideDesign3_ABE_NGA_20 nt_3-9_005_- 31951227_spCas9	mUsmCsmUsCACCUIUAUCCCCAUUCUGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	889
GuideDesign3_ABE_NGA_20 nt_3-9_005_- 31951227_spCas9	mUsmCsmUsCACCUIUAUCCCCAUUCUGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	890
GuideDesign3_ABE_NGA_20 nt_3-9_005_- 31951591_spCas9	mGsmAsmGsGACUCACUUGAAUGAAAGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	891
GuideDesign3_ABE_NGA_20 nt_3-9_005_- 31951591_spCas9	mGsmAsmGsGACUCACUUGAAUGAAAGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	892
GuideDesign3_ABE_NGA_20 nt_3-9_005_+ 31947000_spCas9	mUsmCsmAsAAGCAAUCCACUGUCCAGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	893
GuideDesign3_ABE_NGA_20 nt_3-9_005_+ 31947000_spCas9	mUsmCsmAsAAGCAAUCCACUGUCCAGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	894
GuideDesign3_ABE_NGA_20 nt_3-9_005_+ 31947734_spCas9	mCsmUsmCsCCAGACUCCUUAUGUAGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	895
GuideDesign3_ABE_NGA_20 nt_3-9_005_+ 31947734_spCas9	mCsmUsmCsCCAGACUCCUUAUGUAGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	896
GuideDesign3_ABE_NGA_20 nt_3-9_005_+ 31947939_spCas9	mCsmCsmCsAGGGGAACAACAGAAGCGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	897
GuideDesign3_ABE_NGA_20 nt_3-9_005_+ 31947939_spCas9	mCsmCsmCsAGGGGAACAACAGAAGCGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	898
GuideDesign3_ABE_NGA_20 nt_3-9_005_+ 31948369_spCas9	mAsmCsmAsGGUGGCAAGUUAUGGUGGUUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	899

GuideDesign3_ABE_NGA_20 nt_3- 9_005 + 31948369 spCas9	mAsmCsmAsGGUGGCAAGUUAUGGUGGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	900
GuideDesign3_ABE_NGA_20 nt_3- 9_005 + 31950044 spCas9	mGsmCsmCsAGAUGAAAGCCAGUCUCGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	901
GuideDesign3_ABE_NGA_20 nt_3- 9_005 + 31950044 spCas9	mGsmCsmCsAGAUGAAAGCCAGUCUCGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	902
GuideDesign3_ABE_NGA_20 nt_3- 9_005 + 31950277 spCas9	mGsmUsmCsCCCAGCGCCCUCAAAGGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	903
GuideDesign3_ABE_NGA_20 nt_3- 9_005 + 31950277 spCas9	mGsmUsmCsCCCAGCGCCCUCAAAGGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	904
GuideDesign3_ABE_NGA_20 nt_3- 9_005 + 31951335 spCas9	mUsmAsmCsAGAAAGGCAGCUGUGAGGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	905
GuideDesign3_ABE_NGA_20 nt_3- 9_005 + 31951335 spCas9	mUsmAsmCsAGAAAGGCAGCUGUGAGGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	906
GuideDesign3_ABE_NGC_20 nt_3-9_008_- 31946270 spCas9	mUsmCsmGsCUUACCUCAGACAAGAGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	907
GuideDesign3_ABE_NGC_20 nt_3-9_008_- 31946270 spCas9	mUsmCsmGsCUUACCUCAGACAAGAGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	908
GuideDesign3_ABE_NGC_20 nt_3-9_008_- 31947173 spCas9	mUsmCsmAsCCUCCGUUGUCACAGAUGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	909
GuideDesign3_ABE_NGC_20 nt_3-9_008_- 31947173 spCas9	mUsmCsmAsCCUCCGUUGUCACAGAUGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	910
GuideDesign3_ABE_NGC_20 nt_3-9_008_- 31950129 spCas9	mCsmUsmUsACAAUGACUGAGAUCUUGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	911
GuideDesign3_ABE_NGC_20 nt_3-9_008_- 31950129 spCas9	mCsmUsmUsACAAUGACUGAGAUCUUGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	912
GuideDesign3_ABE_NGC_20 nt_3-9_008_- 31950759 spCas9	mAsmCsmGsCUCUCACCUGAUAGUCUGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	913
GuideDesign3_ABE_NGC_20 nt_3-9_008_- 31950759 spCas9	mAsmCsmGsCUCUCACCUGAUAGUCUGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	914
GuideDesign3_ABE_NGC_20 nt_3- 9_008 + 31949236 spCas9	mCsmUsmGsCAGGAUUGCACAACAUGGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	915
GuideDesign3_ABE_NGC_20 nt_3- 9_008 + 31949236 spCas9	mCsmUsmGsCAGGAUUGCACAACAUGGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	916
GuideDesign3_ABE_NGC_20 nt_3- 9_008 + 31950863 spCas9	mAsmUsmAsGGCCCAUUUGUCUCCCCGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	917

GuideDesign3_ABE_NGC_20 nt_3- 9_008 + 31950863_spCas9	mAsmUsmAsGGCCCAUUUGUCUCCCCGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	918
GuideDesign3_ABE_NGC_20 nt_3- 9_008 + 31951866_spCas9	mCsmUsmCsUGCAGGUUGGUGUAUUCGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	919
GuideDesign3_ABE_NGC_20 nt_3- 9_008 + 31951866_spCas9	mCsmUsmCsUGCAGGUUGGUGUAUUCGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	920
GuideDesign3_ABE_NGG_20 nt_3-9_002_- 31946271_spCas9	mCsmUsmCsGCUUACCUCAGACAAGGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	921
GuideDesign3_ABE_NGG_20 nt_3-9_002_- 31946271_spCas9	mCsmUsmCsGCUUACCUCAGACAAGGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	922
GuideDesign3_ABE_NGG_20 nt_3-9_002_- 31947508_spCas9	mCsmAsmAsAGGUCACCUUGGCAGGAGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	923
GuideDesign3_ABE_NGG_20 nt_3-9_002_- 31947508_spCas9	mCsmAsmAsAGGUCACCUUGGCAGGAGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	924
GuideDesign3_ABE_NGG_20 nt_3-9_002_- 31948947_spCas9	mCsmCsmUsUCUGACCAUCAGUCAUGGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	925
GuideDesign3_ABE_NGG_20 nt_3-9_002_- 31948947_spCas9	mCsmCsmUsUCUGACCAUCAGUCAUGGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	926
GuideDesign3_ABE_NGG_20 nt_3-9_002_- 31949325_spCas9	mUsmCsmAsCCCAGAUAAUCCUCCUGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	927
GuideDesign3_ABE_NGG_20 nt_3-9_002_- 31949325_spCas9	mUsmCsmAsCCCAGAUAAUCCUCCUGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	928
GuideDesign3_ABE_NGG_20 nt_3-9_002_- 31950130_spCas9	mGsmCsmUsUACAAUGACUGAGAUCUGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	929
GuideDesign3_ABE_NGG_20 nt_3-9_002_- 31950130_spCas9	mGsmCsmUsUACAAUGACUGAGAUCUGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	930
GuideDesign3_ABE_NGG_20 nt_3-9_002_- 31950926_spCas9	mCsmUsmUsACUUUGUUGCUGGCAAGGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	931
GuideDesign3_ABE_NGG_20 nt_3-9_002_- 31950926_spCas9	mCsmUsmUsACUUUGUUGCUGGCAAGGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	932
GuideDesign3_ABE_NGG_20 nt_3-9_002_- 31951456_spCas9	mUsmCsmUsCACCUCUGCAAGUAUUGGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	933
GuideDesign3_ABE_NGG_20 nt_3-9_002_- 31951456_spCas9	mUsmCsmUsCACCUCUGCAAGUAUUGGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	934
GuideDesign3_ABE_NGG_20 nt_3- 9_002 + 31948364_spCas9	mCsmAsmCsCCACAGGUGGCAAGUUAGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	935

GuideDesign3_ABE_NGG_20 nt_3- 9_002 + 31948364_spCas9	mCsmAsmCsCCACAGUGGCAAGUUAGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	936
GuideDesign3_ABE_NGG_20 nt_3- 9_002 + 31948825_spCas9	mAsmCsmAsGACCACAAGUUGAAGUCGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	937
GuideDesign3_ABE_NGG_20 nt_3- 9_002 + 31948825_spCas9	mAsmCsmAsGACCACAAGUUGAAGUCGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	938
GuideDesign3_ABE_NGG_20 nt_3- 9_002 + 31949235_spCas9	mUsmCsmUsGCAGGAUUGCACAACAUGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	939
GuideDesign3_ABE_NGG_20 nt_3- 9_002 + 31949235_spCas9	mUsmCsmUsGCAGGAUUGCACAACAUGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	940
GuideDesign3_ABE_NGG_20 nt_3- 9_002 + 31949238_spCas9	mGsmCsmAsGGAUUGCACAACAUGGGGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	941
GuideDesign3_ABE_NGG_20 nt_3- 9_002 + 31949238_spCas9	mGsmCsmAsGGAUUGCACAACAUGGGGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	942
GuideDesign3_ABE_NGG_20 nt_3- 9_002 + 31949412_spCas9	mCsmCsmCsUCAGAUGUCUAUGUGUUGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	943
GuideDesign3_ABE_NGG_20 nt_3- 9_002 + 31949412_spCas9	mCsmCsmCsUCAGAUGUCUAUGUGUUGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	944
GuideDesign3_ABE_NGG_20 nt_3- 9_002 + 31949413_spCas9	mCsmCsmUsCAGAUGUCUAUGUGUUUGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	945
GuideDesign3_ABE_NGG_20 nt_3- 9_002 + 31949413_spCas9	mCsmCsmUsCAGAUGUCUAUGUGUUUGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	946
GuideDesign3_ABE_NGG_20 nt_3- 9_002 + 31949414_spCas9	mCsmUsmCsAGAUGUCUAUGUGUUUGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	947
GuideDesign3_ABE_NGG_20 nt_3- 9_002 + 31949414_spCas9	mCsmUsmCsAGAUGUCUAUGUGUUUGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	948
GuideDesign3_ABE_NGG_20 nt_3- 9_002 + 31950275_spCas9	mGsmUsmGsUCCCCAGCGCCCUUCAAGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	949
GuideDesign3_ABE_NGG_20 nt_3- 9_002 + 31950275_spCas9	mGsmUsmGsUCCCCAGCGCCCUUCAAGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	950
GuideDesign3_ABE_NGG_20 nt_3- 9_002 + 31950276_spCas9	mUsmGsmUsCCCCAGCGCCCUUCAAGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	951
GuideDesign3_ABE_NGG_20 nt_3- 9_002 + 31950276_spCas9	mUsmGsmUsCCCCAGCGCCCUUCAAGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	952
GuideDesign3_ABE_NGG_20 nt_3- 9_002 + 31950609_spCas9	mCsmUsmAsCUUCAGGAGGGGAGAAGGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	953

GuideDesign3_ABE_NGG_20 nt_3- 9_002 + 31950609_spCas9	mCsmUsmAsCUUCAGGAGGGGAGAAGGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	954
GuideDesign3_ABE_NGG_20 nt_3- 9_002 + 31950610_spCas9	mUsmAsmCsUUCAGGAGGGGAGAAGCGUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	955
GuideDesign3_ABE_NGG_20 nt_3- 9_002 + 31950610_spCas9	mUsmAsmCsUUCAGGAGGGGAGAAGCGUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	956
GuideDesign3_ABE_NGG_20 nt_3- 9_002 + 31951544_spCas9	mCsmUsmCsCUUCAGGUGAUUCUGGGUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	957
GuideDesign3_ABE_NGG_20 nt_3- 9_002 + 31951544_spCas9	mCsmUsmCsCUUCAGGUGAUUCUGGGUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	958
GuideDesign3_ABE_NGG_20 nt_3- 9_002 + 31951869_spCas9	mUsmGsmCsAGGUUGGUGUAAUCAGCGUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	959
GuideDesign3_ABE_NGG_20 nt_3- 9_002 + 31951869_spCas9	mUsmGsmCsAGGUUGGUGUAAUCAGCGUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	960
GuideDesign3_ABE_NGG_20 nt_3- 9_002 + 31951870_spCas9	mGsmCsmAsGGUUGGUGUAAUCAGCUGUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	961
GuideDesign3_ABE_NGG_20 nt_3- 9_002 + 31951870_spCas9	mGsmCsmAsGGUUGGUGUAAUCAGCUGUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	962
GuideDesign3_ABE_NNGRR T_21nt_5-14_011_- _31948945_saCas9	mUsmCsmCsCUUCUGACCAUCAGUCAUGUUUAGUACUCU GUAAUGAAAAUUAACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsm U	963
GuideDesign3_ABE_NNGRR T_21nt_5-14_011_- _31948945_saCas9	mUsmCsmCsCUUCUGACCAUCAGUCAUGUUUAGUACUCU GUAAUGAAAAUUAACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsm U	964
GuideDesign3_ABE_NNGRR T_21nt_5-14_011_- _31949323_saCas9	mAsmCsmUsCACCCAGAUAAUCCUCCCGUUUAGUACUCU GUAAUGAAAAUUAACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsm U	965
GuideDesign3_ABE_NNGRR T_21nt_5-14_011_- _31949323_saCas9	mAsmCsmUsCACCCAGAUAAUCCUCCCGUUUAGUACUCU GUAAUGAAAAUUAACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsm U	966
GuideDesign3_ABE_NNGRR T_21nt_5-14_011_- _31950382_saCas9	mCsmCsmUsUACCUACGCUGACCUUGAGUUUAGUACUCU GUAAUGAAAAUUAACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsm U	967
GuideDesign3_ABE_NNGRR T_21nt_5-14_011_- _31950382_saCas9	mCsmCsmUsUACCUACGCUGACCUUGAGUUUAGUACUCU GUAAUGAAAAUUAACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsm U	968
GuideDesign3_ABE_NNGRR T_21nt_5-14_011_- _31951455_saCas9	mUsmUsmCsUCUCACCUCUGCAAGUAUGUUUAGUACUCU GUAAUGAAAAUUAACAGAAUCUACUAAAACAAGGCAAAAUG	969

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GuideDesign3_ABE_NNGRR T_21nt_5- 14_011_+_31949411_saCas9	mUsmCsmCsCUCAGAUGUCUAUGUGUUGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	971
GuideDesign3_ABE_NNGRR T_21nt_5- 14_011_+_31949411_saCas9	mUsmCsmCsCUCAGAUGUCUAUGUGUUGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	972
GuideDesign3_ABE_NNGRR T_21nt_5- 14_011_+_31950042_saCas9	mCsmUsmGsCCAGAUGAAAGCCAGUCUGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	973
GuideDesign3_ABE_NNGRR T_21nt_5- 14_011_+_31950042_saCas9	mCsmUsmGsCCAGAUGAAAGCCAGUCUGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	974
GuideDesign3_ABE_NNNRR T_21nt_5-14_014_- _31947176_saCas9	mAsmUsmGsCUUCUCACCUCCGUUGUCGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	975
GuideDesign3_ABE_NNNRR T_21nt_5-14_014_- _31947176_saCas9	mAsmUsmGsCUUCUCACCUCCGUUGUCGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	976
GuideDesign3_ABE_NNNRR T_21nt_5-14_014_- _31948067_saCas9	mAsmGsmGsAGGAUUCACCUCUUCUAGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	977
GuideDesign3_ABE_NNNRR T_21nt_5-14_014_- _31948067_saCas9	mAsmGsmGsAGGAUUCACCUCUUCUAGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	978
GuideDesign3_ABE_NNNRR T_21nt_5-14_014_- _31948499_saCas9	mCsmCsmCsUAACCUCUGACCUUCAUAGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	979
GuideDesign3_ABE_NNNRR T_21nt_5-14_014_- _31948499_saCas9	mCsmCsmCsUAACCUCUGACCUUCAUAGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	980
GuideDesign3_ABE_NNNRR T_21nt_5-14_014_- _31948942_saCas9	mCsmUsmUsCUGACCAUCAGUCAUGAGGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	981
GuideDesign3_ABE_NNNRR T_21nt_5-14_014_- _31948942_saCas9	mCsmUsmUsCUGACCAUCAGUCAUGAGGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	982

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GuideDesign3_ABE_NNNRR T_21nt_5-14_014_- _31950135_saCas9	mGsmGsmAsUUCUGUGCUUACAAUGACGUUUUAGUACUCU GUA AUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCACUUGUUGGCGAGAUsmUsmUsm U	985
GuideDesign3_ABE_NNNRR T_21nt_5-14_014_- _31950135_saCas9	mGsmGsmAsUUCUGUGCUUACAAUGACGUUUUAGUACUCU GUA AUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCACUUGUUGGCGAGAUsmUsmUsm U	986
GuideDesign3_ABE_NNNRR T_21nt_5-14_014_- _31950387_saCas9	mUsmGsmCsAUCCUUACCUACGCUGACGUUUUAGUACUCU GUA AUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCACUUGUUGGCGAGAUsmUsmUsm U	987
GuideDesign3_ABE_NNNRR T_21nt_5-14_014_- _31950387_saCas9	mUsmGsmCsAUCCUUACCUACGCUGACGUUUUAGUACUCU GUA AUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCACUUGUUGGCGAGAUsmUsmUsm U	988
GuideDesign3_ABE_NNNRR T_21nt_5-14_014_- _31950925_saCas9	mUsmGsmUsCUUACUUUGUUGCUGGCAGUUUUAGUACUCU GUA AUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCACUUGUUGGCGAGAUsmUsmUsm U	989
GuideDesign3_ABE_NNNRR T_21nt_5-14_014_- _31950925_saCas9	mUsmGsmUsCUUACUUUGUUGCUGGCAGUUUUAGUACUCU GUA AUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCACUUGUUGGCGAGAUsmUsmUsm U	990
GuideDesign3_ABE_NNNRR T_21nt_5-14_014_- _31950928_saCas9	mGsmUsmAsUGUCUUACUUUGUUGCUGGUUUUAGUACUCU GUA AUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCACUUGUUGGCGAGAUsmUsmUsm U	991
GuideDesign3_ABE_NNNRR T_21nt_5-14_014_- _31950928_saCas9	mGsmUsmAsUGUCUUACUUUGUUGCUGGUUUUAGUACUCU GUA AUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCACUUGUUGGCGAGAUsmUsmUsm U	992
GuideDesign3_ABE_NNNRR T_21nt_5-14_014_+_31946366_saCas9	mCsmUsmUsCAGGUGUGACCACCACUCGUUUUAGUACUCU GUA AUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCACUUGUUGGCGAGAUsmUsmUsm U	993
GuideDesign3_ABE_NNNRR T_21nt_5-14_014_+_31946366_saCas9	mCsmUsmUsCAGGUGUGACCACCACUCGUUUUAGUACUCU GUA AUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCACUUGUUGGCGAGAUsmUsmUsm U	994
GuideDesign3_ABE_NNNRR T_21nt_5-14_014_+_31948817_saCas9	mCsmCsmCsUCUCCACAGACCACAAGUGUUUUAGUACUCU GUA AUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCACUUGUUGGCGAGAUsmUsmUsm U	995
GuideDesign3_ABE_NNNRR T_21nt_5-14_014_+_31948817_saCas9	mCsmCsmCsUCUCCACAGACCACAAGUGUUUUAGUACUCU GUA AUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG	996

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GuideDesign3_ABE_NNNRR T_21nt_5- 14_014+_31951334_saCas9	mCsmUsmAsCAGAAAGGCAGCUGUGAGGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	998
GuideDesign3_CBE_NNGRR T_21nt_3-12_012_- _31947927_saCas9	mUsmGsmUsUGUUCUCCUGGGUGCCAGGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	999
GuideDesign3_CBE_NNGRR T_21nt_3-12_012_- _31947927_saCas9	mUsmGsmUsUGUUCUCCUGGGUGCCAGGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	1000
GuideDesign3_CBE_NNGRR T_21nt_3-12_012_- _31949397_saCas9	mGsmAsmCsAUCUGAGGGAUAAAAAGGGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	1001
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GuideDesign3_CBE_NNGRR T_21nt_3-12_012_- _31950031_saCas9	mGsmGsmCsUUUCAUCUGGCAGAGAAGGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	1003
GuideDesign3_CBE_NNGRR T_21nt_3-12_012_- _31950031_saCas9	mGsmGsmCsUUUCAUCUGGCAGAGAAGGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	1004
GuideDesign3_CBE_NNGRR T_21nt_3-12_012_- _31951856_saCas9	mUsmAsmCsACCAACCUGCAGAGGCAGGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	1005
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GuideDesign3_CBE_NNNRR T_21nt_3-12_015_- _31946263_saCas9	mCsmUsmUsACCUCCAGACAAGAGGCCGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	1007
GuideDesign3_CBE_NNNRR T_21nt_3-12_015_- _31946263_saCas9	mCsmUsmUsACCUCCAGACAAGAGGCCGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	1008
GuideDesign3_CBE_NNNRR T_21nt_3-12_015_- _31946354_saCas9	mUsmGsmGsUCACACCUGAAGAGAAAGGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	1009

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GuideDesign3_CBE_NNNRR T_21nt_3-12_015_- _31946985_saCas9	mGsmGsmAsUUGCUUUGAGAAGGGGGGGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCACUUGUUGGCGAGAUsmUsmUsm U	1012
GuideDesign3_CBE_NNNRR T_21nt_3-12_015_- _31947322_saCas9	mCsmGsmCsUGCAGAGGUAUGAGACAUGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCACUUGUUGGCGAGAUsmUsmUsm U	1013
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GuideDesign3_CBE_NNNRR T_21nt_3-12_015_- _31947724_saCas9	mAsmUsmGsAAGGAGUCUGGGAGAGUCGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCACUUGUUGGCGAGAUsmUsmUsm U	1018
GuideDesign3_CBE_NNNRR T_21nt_3-12_015_- _31950269_saCas9	mUsmUsmUsGAAGGGCGCUGGGGACACGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCACUUGUUGGCGAGAUsmUsmUsm U	1019
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GuideDesign3_CBE_NNNRR T_21nt_3-12_015_- _31950922_saCas9	mCsmUsmUsACUUUGUUGCUGGCAAGUGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG	1023

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GuideDesign3_CBE_NNNRR T_21nt_3-12_015_- _31950922_saCas9	mCsmUsmUsACUUUGUUGCUGGCAAGUGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	1024
GuideDesign10_CBE_NGC_2 Ont_4-9_009_- _31947141_spCas9	mAsmCsmUsCCAUCGGCCAUCACUUGUUUUAGAGCUAGA AAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1025
GuideDesign10_CBE_NGC_2 Ont_4-9_009_- _31948418_spCas9	mAsmCsmCsCAAAUUUUGGGGUAUGUGUUUUAGAGCUAGA AAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1026
GuideDesign10_CBE_NGC_2 Ont_4-9_009_- _31948461_spCas9	mCsmGsmUsGACCCAGUCGCAUUAACGUUUUUAGAGCUAGA AAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1027
GuideDesign10_CBE_NGC_2 Ont_4- 9_009 + 31946572_spCas9	mGsmAsmCsCAAAGACUGUCAGGAAGUUUUAGAGCUAGA AAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1028
GuideDesign10_CBE_NGC_2 Ont_4- 9_009 + 31947152_spCas9	mGsmGsmCsCGAUGGAGUGGGCAGACGUUUUUAGAGCUAGA AAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1029
GuideDesign10_CBE_NGC_2 Ont_4- 9_009 + 31947758_spCas9	mAsmCsmCsCCUCAAGAGGUGGCCGAGUUUUAGAGCUAGA AAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1030
GuideDesign10_CBE_NGC_2 Ont_4- 9_009 + 31948862_spCas9	mAsmGsmGsCCCUCAGGCAGUGUACGUUUUUAGAGCUAGA AAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1031
GuideDesign10_CBE_NGC_2 Ont_4- 9_009 + 31950757_spCas9	mUsmGsmGsCCAGACUUAUCAGGUGAGGUUUUUAGAGCUAGA AAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1032
GuideDesign10_CBE_NGC_2 Ont_4- 9_009 + 31950937_spCas9	mCsmAsmAsCAAAGUAAGACAUACUUGUUUUAGAGCUAGA AAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1033
GuideDesign10_CBE_NGC_2 Ont_4- 9_009 + 31951925_spCas9	mCsmAsmAsAAGCAGGUACCUGCUCAGUUUUAGAGCUAGA AAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1034
GuideDesign10_CBE_NGC_2 Ont_4- 9_009 + 31951966_spCas9	mCsmCsmUsCUUUCAAGUGCUGCCCUGUUUUAGAGCUAGA AAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1035
GuideDesign3_CBE_NNGRR T_21nt_3- 12_012_+_31951994_saCas9	mGsmAsmGsAAACUCCAAGAUGAGGAUGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	1036
GuideDesign3_CBE_NNNRR T_21nt_3-12_015_- _31950102_saCas9	mCsmUsmGsCCAUGGUUGCUUGUGGUAGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	1037
GuideDesign3_CBE_NNNRR T_21nt_3- 12_015_+_31946459_saCas9	mUsmUsmCsUCCAAGAGGGCCAGGCACGUUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	1038
GuideDesign3_CBE_NNNRR T_21nt_3- 12_015_+_31946513_saCas9	mAsmCsmCsCUGUGCAGACACGUACCUGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG	1039

	CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	
GuideDesign3_CBE_NNNRR T_21nt_3- 12_015_+_31946573_saCas9	mAsmCsmCsAAAAGACUGUCAGGAAGGGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	1040
GuideDesign3_CBE_NNNRR T_21nt_3- 12_015_+_31947137_saCas9	mAsmCsmCsUGCCAAGUGAAUGGCCGAGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	1041
GuideDesign3_CBE_NNNRR T_21nt_3- 12_015_+_31949486_saCas9	mAsmGsmAsCAAUGAGCAACAUGUGUUGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	1042
GuideDesign3_CBE_NNNRR T_21nt_3- 12_015_+_31949493_saCas9	mGsmAsmGsCAACAUGUGUCAAAGUCGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	1043
GuideDesign3_CBE_NNNRR T_21nt_3- 12_015_+_31950110_saCas9	mCsmCsmAsCAAGCAACCAUGGCAGGCGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	1044
GuideDesign3_CBE_NNNRR T_21nt_3- 12_015_+_31951909_saCas9	mCsmAsmAsAAACCAGAAGCGGCAAAAGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	1045
GuideDesign3_CBE_NNNRR T_21nt_3- 12_015_+_31951994_saCas9	mGsmAsmGsAAACUCCAAGAUGAGGAUGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	1046
GuideDesign10_CBE_NGA_2 Ont_4-9_006_- 31946539_spCas9	mAsmGsmGsGUGCUCAGGACCCCGUGUUUUAGAGCUAGA AAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1047
GuideDesign10_CBE_NGA_2 Ont_4-9_006_- 31947033_spCas9	mGsmGsmGsCCAGUAUUCGCCGUUCUGUUUUAGAGCUAGA AAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1048
GuideDesign10_CBE_NGA_2 Ont_4-9_006_- 31947477_spCas9	mCsmGsmCsUCCAAGAGCCACCUUCCGUUUUAGAGCUAGA AAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1049
GuideDesign10_CBE_NGA_2 Ont_4-9_006_- 31948907_spCas9	mGsmCsmGsGUUCCAGCCUUCAGGAGGUUUUAGAGCUAGA AAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1050
GuideDesign10_CBE_NGA_2 Ont_4-9_006_- 31950068_spCas9	mGsmUsmUsCCCAAACCAUGCCACAGGUUUUAGAGCUAGA AAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1051
GuideDesign10_CBE_NGA_2 Ont_4-9_006_- 31950070_spCas9	mGsmUsmGsUUCCCAAACCAUGCCACGUUUUAGAGCUAGA AAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1052
GuideDesign10_CBE_NGA_2 Ont_4-9_006_- 31951968_spCas9	mCsmAsmGsCCAGGGCAGCACUUGAAGUUUUAGAGCUAGA AAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1053
GuideDesign10_CBE_NGA_2 Ont_4-9_006_- 31951972_spCas9	mCsmCsmUsUCAGCCAGGGCAGCACUGUUUUAGAGCUAGA AAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1054

GuideDesign10_CBE_NGA_2 Ont_4- 9 006 + 31946404 spCas9	mCsmCsmCsCAGGGAUCCUGCUCUCUGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1055
GuideDesign10_CBE_NGA_2 Ont_4- 9 006 + 31946568 spCas9	mUsmCsmAsAGACCAAAGACUGUCAGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1056
GuideDesign10_CBE_NGA_2 Ont_4- 9 006 + 31947135 spCas9	mGsmCsmAsCCUGCCAAGUGAAUGGCGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1057
GuideDesign10_CBE_NGA_2 Ont_4- 9 006 + 31947139 spCas9	mCsmUsmGsCCAAGUGAAUGGCCGAUGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1058
GuideDesign10_CBE_NGA_2 Ont_4- 9 006 + 31947148 spCas9	mGsmAsmAsUGGCCGAUGGAGUGGGCGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1059
GuideDesign10_CBE_NGA_2 Ont_4- 9 006 + 31947161 spCas9	mAsmGsmUsGGGCAGACAGCGAUCUGGUUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1060
GuideDesign10_CBE_NGA_2 Ont_4- 9 006 + 31947394 spCas9	mGsmGsmCsAGCCAGUACCGCCUUGAGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1061
GuideDesign10_CBE_NGA_2 Ont_4- 9 006 + 31947460 spCas9	mUsmCsmCsCAGCGGCGAACGUGUCAGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1062
GuideDesign10_CBE_NGA_2 Ont_4- 9 006 + 31947474 spCas9	mGsmUsmGsUCAGGAAGGUGGCUCUUGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1063
GuideDesign10_CBE_NGA_2 Ont_4- 9 006 + 31947942 spCas9	mAsmGsmGsGGAACAACAGAAGCGGAGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1064
GuideDesign10_CBE_NGA_2 Ont_4- 9 006 + 31948866 spCas9	mCsmCsmUsCCAGGCAGUGUACAGCAGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1065
GuideDesign10_CBE_NGA_2 Ont_4- 9 006 + 31949541 spCas9	mUsmUsmCsUACCAAUGAUCGGUAGGUUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1066
GuideDesign10_CBE_NGA_2 Ont_4- 9 006 + 31949543 spCas9	mCsmUsmAsCCAAUGAUCGGUAGGGGUUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1067
GuideDesign10_CBE_NGA_2 Ont_4- 9 006 + 31950113 spCas9	mCsmAsmAsGCAACCAUGGCAGGCCAGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1068
GuideDesign10_CBE_NGA_2 Ont_4- 9 006 + 31950755 spCas9	mUsmAsmUsGGCCAGACUAUCAGGUGGUUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1069
GuideDesign10_CBE_NGA_2 Ont_4- 9 006 + 31950927 spCas9	mCsmAsmCsUUGCCAGCAACAAAGUAGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1070
GuideDesign10_CBE_NGA_2 Ont_4- 9 006 + 31951361 spCas9	mGsmCsmUsCAAUAUGCCCCAGGCUAGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1071
GuideDesign10_CBE_NGA_2 Ont_4- 9 006 + 31951969 spCas9	mCsmUsmUsUCAAGUGCUGCCUGGCGUUUUAGAGCUAGA AAUAGCAAGUUAUUUUUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1072

GuideDesign10_CBE_NGG_2 Ont 4-9_003_- 31947142 spCas9	mCsmAsmCsUCCAUCGGCCAUUCACUGUUUUAGAGCUAGA AAUAGCAAGUUAUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1073
GuideDesign10_CBE_NGG_2 Ont 4-9_003_- 31948419 spCas9	mGsmAsmCsCCAAAUUUUGGGGUAUGGUUUUAGAGCUAGA AAUAGCAAGUUAUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1074
GuideDesign10_CBE_NGG_2 Ont 4-9_003_- 31948908 spCas9	mUsmGsmCsGGUUCAGCCUUCAGGAGUUUUAGAGCUAGA AAUAGCAAGUUAUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1075
GuideDesign10_CBE_NGG_2 Ont 4-9_003_- 31948909 spCas9	mGsmUsmGsCGGUUCAGCCUUCAGGGUUUUAGAGCUAGA AAUAGCAAGUUAUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1076
GuideDesign10_CBE_NGG_2 Ont 4-9_003_- 31950110 spCas9	mUsmGsmGsCCUGCCAUGGUUGCUUGGUUUUAGAGCUAGA AAUAGCAAGUUAUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1077
GuideDesign10_CBE_NGG_2 Ont 4- 9_003 + 31946448 spCas9	mCsmUsmCsCUUCCGACUUCUCCAAGGUUUUAGAGCUAGA AAUAGCAAGUUAUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1078
GuideDesign10_CBE_NGG_2 Ont 4- 9_003 + 31946449 spCas9	mUsmCsmCsUUCCGACUUCUCCAAGAGUUUUAGAGCUAGA AAUAGCAAGUUAUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1079
GuideDesign10_CBE_NGG_2 Ont 4- 9_003 + 31946460 spCas9	mUsmCsmUsCCAAGAGGGCCAGGCACGUUUUAGAGCUAGA AAUAGCAAGUUAUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1080
GuideDesign10_CBE_NGG_2 Ont 4- 9_003 + 31946567 spCas9	mCsmUsmCsAAGACCAAAAGACUGUCGUUUUAGAGCUAGA AAUAGCAAGUUAUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1081
GuideDesign10_CBE_NGG_2 Ont 4- 9_003 + 31946571 spCas9	mAsmGsmAsCCAAAGACUGUCAGGAGUUUUAGAGCUAGA AAUAGCAAGUUAUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1082
GuideDesign10_CBE_NGG_2 Ont 4- 9_003 + 31947138 spCas9	mCsmCsmUsGCCAAGUGAAUGGCCGAGUUUUAGAGCUAGA AAUAGCAAGUUAUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1083
GuideDesign10_CBE_NGG_2 Ont 4- 9_003 + 31947459 spCas9	mCsmUsmCsCCAGCGGCGAACGUGUCGUUUUAGAGCUAGA AAUAGCAAGUUAUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1084
GuideDesign10_CBE_NGG_2 Ont 4- 9_003 + 31947463 spCas9	mCsmAsmGsCGGCGAACGUGUCAGGAGUUUUAGAGCUAGA AAUAGCAAGUUAUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1085
GuideDesign10_CBE_NGG_2 Ont 4- 9_003 + 31947466 spCas9	mCsmGsmGsCGAACGUGUCAGGAAGGGUUUUAGAGCUAGA AAUAGCAAGUUAUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1086
GuideDesign10_CBE_NGG_2 Ont 4- 9_003 + 31947473 spCas9	mCsmGsmUsGUCAGGAAGGUGGCUCUGUUUUAGAGCUAGA AAUAGCAAGUUAUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1087
GuideDesign10_CBE_NGG_2 Ont 4- 9_003 + 31949539 spCas9	mUsmUsmUsUCUACCAAAUGAUCGGUGUUUUAGAGCUAGA AAUAGCAAGUUAUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1088
GuideDesign10_CBE_NGG_2 Ont 4- 9_003 + 31949540 spCas9	mUsmUsmUsCUACCAAAUGAUCGGUAGUUUUAGAGCUAGA AAUAGCAAGUUAUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1089
GuideDesign10_CBE_NGG_2 Ont 4- 9_003 + 31950936 spCas9	mGsmCsmAsACAAAGUAAGACAUACUGUUUUAGAGCUAGA AAUAGCAAGUUAUAAAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1090

GuideDesign10_CBE_NGG_2 0nt_4- 9_003 + 31951965_spCas9	mAsmCsmCsUCUUUCAAGUGCUGCCCGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1091
GuideDesign10_CBE_NGG_2 0nt_4- 9_003 + 31951996_spCas9	mGsmAsmAsACUCCAAGAUGAGGAUUUGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1092
GuideDesign10_CBE_NGG_2 0nt_4- 9_003 + 31951997_spCas9	mAsmAsmAsCUCCAAGAUGAGGAUUUGUUUUAGAGCUAGA AAUAGCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAACUUGA AAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU	1093
GuideDesign3_CBE_NNGRR T_21nt_3- 12_012+_31946459_saCas9	mUsmUsmCsUCCAAGAGGGCCAGGCACGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsm U	1094
GuideDesign3_CBE_NNGRR T_21nt_3- 12_012+_31946459_saCas9	mUsmUsmCsUCCAAGAGGGCCAGGCACGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsm U	1095
GuideDesign3_CBE_NNGRR T_21nt_3- 12_012+_31946573_saCas9	mAsmCsmCsAAAAGACUGUCAGGAAGGGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsm U	1096
GuideDesign3_CBE_NNGRR T_21nt_3- 12_012+_31946573_saCas9	mAsmCsmCsAAAAGACUGUCAGGAAGGGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsm U	1097
GuideDesign3_CBE_NNGRR T_21nt_3- 12_012+_31947137_saCas9	mAsmCsmCsUGCCAAGUGAAUGGCCGAGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsm U	1098
GuideDesign3_CBE_NNGRR T_21nt_3- 12_012+_31947137_saCas9	mAsmCsmCsUGCCAAGUGAAUGGCCGAGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsm U	1099
GuideDesign3_CBE_NNGRR T_21nt_3- 12_012+_31949493_saCas9	mGsmAsmGsCAACAUGUGUCAAAGUCGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsm U	1100
GuideDesign3_CBE_NNGRR T_21nt_3- 12_012+_31949493_saCas9	mGsmAsmGsCAACAUGUGUCAAAGUCGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsm U	1101
GuideDesign3_CBE_NNNRR T_21nt_3-12_015_- _31946530_saCas9	mGsmCsmUsCCAGGACCCCGUAGAUCUGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsm U	1102
GuideDesign3_CBE_NNNRR T_21nt_3-12_015_- _31946530_saCas9	mGsmCsmUsCCAGGACCCCGUAGAUCUGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsm U	1103
GuideDesign3_CBE_NNNRR T_21nt_3-12_015_- _31946538_saCas9	mUsmUsmCsAGGGUGCUCCAGGACCCCGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsm U	1104

GuideDesign3_CBE_NNNRR T_21nt_3-12_015_- _31946538_saCas9	mUsmUsmCsAGGGUGCUCCAGGACCCCGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCACUUGUUGGCGAGAUsmUsmUsm U	1105
GuideDesign3_CBE_NNNRR T_21nt_3-12_015_- _31947030_saCas9	mGsmGsmGsGCCAGUAUUCGGUUCUGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCACUUGUUGGCGAGAUsmUsmUsm U	1106
GuideDesign3_CBE_NNNRR T_21nt_3-12_015_- _31947030_saCas9	mGsmGsmGsGCCAGUAUUCGGUUCUGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCACUUGUUGGCGAGAUsmUsmUsm U	1107
GuideDesign3_CBE_NNNRR T_21nt_3-12_015_- _31947137_saCas9	mAsmCsmUsCCAUCGGCCAUCACUUGGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCACUUGUUGGCGAGAUsmUsmUsm U	1108
GuideDesign3_CBE_NNNRR T_21nt_3-12_015_- _31947137_saCas9	mAsmCsmUsCCAUCGGCCAUCACUUGGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCACUUGUUGGCGAGAUsmUsmUsm U	1109
GuideDesign3_CBE_NNNRR T_21nt_3-12_015_- _31950106_saCas9	mUsmGsmGsCCUGCCAUGGUUGCUUGUGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCACUUGUUGGCGAGAUsmUsmUsm U	1110
GuideDesign3_CBE_NNNRR T_21nt_3-12_015_- _31950106_saCas9	mUsmGsmGsCCUGCCAUGGUUGCUUGUGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCACUUGUUGGCGAGAUsmUsmUsm U	1111
GuideDesign3_CBE_NNNRR T_21nt_3-12_015_- _31950109_saCas9	mUsmCsmUsUGGCCUGCCAUGGUUGCUUGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCACUUGUUGGCGAGAUsmUsmUsm U	1112
GuideDesign3_CBE_NNNRR T_21nt_3-12_015_- _31950109_saCas9	mUsmCsmUsUGGCCUGCCAUGGUUGCUUGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCACUUGUUGGCGAGAUsmUsmUsm U	1113
GuideDesign3_CBE_NNNRR T_21nt_3-12_015_- _31951965_saCas9	mUsmCsmAsGCCAGGGCAGCACUUGAAGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCACUUGUUGGCGAGAUsmUsmUsm U	1114
GuideDesign3_CBE_NNNRR T_21nt_3-12_015_- _31951965_saCas9	mUsmCsmAsGCCAGGGCAGCACUUGAAGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCACUUGUUGGCGAGAUsmUsmUsm U	1115
GuideDesign3_CBE_NNNRR T_21nt_3- 12_015_+_31947132_saCas9	mAsmUsmCsGCACCUGCCAAGUGAAGGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCACUUGUUGGCGAGAUsmUsmUsm U	1116
GuideDesign3_CBE_NNNRR T_21nt_3- 12_015_+_31947132_saCas9	mAsmUsmCsGCACCUGCCAAGUGAAGGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCACUUGUUGGCGAGAUsmUsmUsm U	1117
GuideDesign3_CBE_NNNRR T_21nt_3- 12_015_+_31947151_saCas9	mUsmGsmGsCCGAUGGAGUGGGCAGACGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG	1118

	CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	
GuideDesign3_CBE_NNNRR T_21nt_3- 12_015+_31947151_saCas9	mUsmGsmGsCCGAUGGAGUGGGCAGACGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	1119
GuideDesign3_CBE_NNNRR T_21nt_3- 12_015+_31947460_saCas9	mUsmCsmCsCAGCGGCGAACGUGUCAGGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	1120
GuideDesign3_CBE_NNNRR T_21nt_3- 12_015+_31947460_saCas9	mUsmCsmCsCAGCGGCGAACGUGUCAGGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	1121
GuideDesign3_CBE_NNNRR T_21nt_3- 12_015+_31947939_saCas9	mCsmCsmCsAGGGGAACAACAGAAGCGGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	1122
GuideDesign3_CBE_NNNRR T_21nt_3- 12_015+_31947939_saCas9	mCsmCsmCsAGGGGAACAACAGAAGCGGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	1123
GuideDesign3_CBE_NNNRR T_21nt_3- 12_015+_31948478_saCas9	mGsmUsmCsACGAAGCAGCUCAAUGAAGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	1124
GuideDesign3_CBE_NNNRR T_21nt_3- 12_015+_31948478_saCas9	mGsmUsmCsACGAAGCAGCUCAAUGAAGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	1125
GuideDesign3_CBE_NNNRR T_21nt_3- 12_015+_31948863_saCas9	mGsmGsmCsCCUCCAGGCAGUGUACAGGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	1126
GuideDesign3_CBE_NNNRR T_21nt_3- 12_015+_31948863_saCas9	mGsmGsmCsCCUCCAGGCAGUGUACAGGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	1127
GuideDesign3_CBE_NNNRR T_21nt_3- 12_015+_31949540_saCas9	mUsmUsmUsCUACCAAUGAUCGGUAGGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	1128
GuideDesign3_CBE_NNNRR T_21nt_3- 12_015+_31949540_saCas9	mUsmUsmUsCUACCAAUGAUCGGUAGGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	1129
GuideDesign3_CBE_NNNRR T_21nt_3- 12_015+_31950116_saCas9	mGsmCsmAsACCAUGGCAGGCCAAGAUGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	1130
GuideDesign3_CBE_NNNRR T_21nt_3- 12_015+_31950116_saCas9	mGsmCsmAsACCAUGGCAGGCCAAGAUGUUUUAGUACUCU GUAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAAUG CCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	1131

Table 1D: Representative sequences for guide polynucleotides for use in guiding a base editor to alter a start codon or TATA box of a complement factor B polynucleotide using base editing.⁴

Guide polynucleotide name	Guide polynucleotide sequence	SEQ ID NO
GuideDesign90_ABE_NGA_20nt_3-12 019 + 31946067 spCas9	mAsmAsmAsAGGCUGGGGGCUGGUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1132
GuideDesign90_CBE_NGA_20nt_4-9 006 + 31946067 spCas9	mAsmAsmAsAGGCUGGGGGCUGGUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1133
GuideDesign90_CBE_NGA_20nt_3-16 035 + 31946067 spCas9	mAsmAsmAsAGGCUGGGGGCUGGUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1134
GuideDesign90_ABE_NG_20nt_3-9 027 + 31946067 spCas9	mAsmAsmAsAGGCUGGGGGCUGGUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1135
GuideDesign90_CBE_NG_20nt_4-9 028 + 31946067 spCas9	mAsmAsmAsAGGCUGGGGGCUGGUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1136
GuideDesign90_ABE_NRN_20nt_3-9 021 + 31946067 spCas9	mAsmAsmAsAGGCUGGGGGCUGGUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1137
GuideDesign90_CBE_NRN_20nt_3-9 022 + 31946067 spCas9	mAsmAsmAsAGGCUGGGGGCUGGUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1138
GuideDesign90_MBE_NRN_20nt_3-9 023 + 31946067 spCas9	mAsmAsmAsAGGCUGGGGGCUGGUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1139
GuideDesign90_ABE_NRN_20nt_3-9 021 + 31946068 spCas9	mAsmAsmAsGGCUGGGGGCUGGUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1140
GuideDesign90_CBE_NRN_20nt_3-9 022 + 31946068 spCas9	mAsmAsmAsGGCUGGGGGCUGGUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1141
GuideDesign90_MBE_NRN_20nt_3-9 023 + 31946068 spCas9	mAsmAsmAsGGCUGGGGGCUGGUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1142
GuideDesign90_CBE_NRRH_20nt_3-9 031 + 31946068 spCas9	mAsmAsmAsGGCUGGGGGCUGGUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1143
GuideDesign90_ABE_NGC_20nt_3-9 008 + 31946069 spCas9	mAsmAsmGsGUGGGGGCUGGUGGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1144
GuideDesign90_ABE_NGC_20nt_3-12 020 + 31946069 spCas9	mAsmAsmGsGUGGGGGCUGGUGGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1145

⁴ “mN” indicates a 2'-OMe modification of the nucleotide “N”, and “Ns” indicates that the nucleotide “N” is linked to the following (i.e., 3') nucleotide by a phosphorothioate (PS).

Guide polynucleotide name	Guide polynucleotide sequence	SEQ ID NO
GuideDesign90_CBE_NGC_20nt_4-9_009 + 31946069_spCas9	mAsmAsmGsGCUGGGGGCUGGUGGGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1146
GuideDesign90_ABE_NG_20nt_3-9_027 + 31946069_spCas9	mAsmAsmGsGCUGGGGGCUGGUGGGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1147
GuideDesign90_CBE_NG_20nt_4-9_028 + 31946069_spCas9	mAsmAsmGsGCUGGGGGCUGGUGGGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1148
GuideDesign90_ABE_NRN_20nt_3-9_021 + 31946069_spCas9	mAsmAsmGsGCUGGGGGCUGGUGGGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1149
GuideDesign90_CBE_NRN_20nt_3-9_022 + 31946069_spCas9	mAsmAsmGsGCUGGGGGCUGGUGGGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1150
GuideDesign90_MBE_NRN_20nt_3-9_023 + 31946069_spCas9	mAsmAsmGsGCUGGGGGCUGGUGGGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1151
GuideDesign90_ABE_NRCH_20nt_3-9_024 + 31946069_spCas9	mAsmAsmGsGCUGGGGGCUGGUGGGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1152
GuideDesign90_CBE_NRCH_20nt_3-9_030 + 31946069_spCas9	mAsmAsmGsGCUGGGGGCUGGUGGGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1153
GuideDesign90_ABE_NGG_20nt_3-12_018_-31946040_spCas9	mAsmAsmUsCUGUGUUCUGGCACCUGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1154
GuideDesign90_CBE_NGG_20nt_4-9_003_-31946040_spCas9	mAsmAsmUsCUGUGUUCUGGCACCUGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1155
GuideDesign90_CBE_NGG_20nt_3-9_029_-31946040_spCas9	mAsmAsmUsCUGUGUUCUGGCACCUGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1156
GuideDesign90_CBE_NGG_20nt_3-16_033_-31946040_SpCas9	mAsmAsmUsCUGUGUUCUGGCACCUGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1157
GuideDesign90_ABE_NG_20nt_3-9_027_-31946041_spCas9	mAsmAsmUsCUGUGUUCUGGCACCUGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1158
GuideDesign90_CBE_NG_20nt_4-9_028_-31946041_spCas9	mAsmAsmUsCUGUGUUCUGGCACCUGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1159
GuideDesign90_ABE_NRN_20nt_3-9_021_-31946040_spCas9	mAsmAsmUsCUGUGUUCUGGCACCUGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1160
GuideDesign90_CBE_NRN_20nt_3-9_022_-31946040_spCas9	mAsmAsmUsCUGUGUUCUGGCACCUGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1161
GuideDesign90_MBE_NRN_20nt_3-9_023_-31946040_spCas9	mAsmAsmUsCUGUGUUCUGGCACCUGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1162

Guide polynucleotide name	Guide polynucleotide sequence	SEQ ID NO
GuideDesign90_CBE_NRRH_20nt_3-9_031_-31946039_spCas9	mAsmAsmUsCUGUGUUCUGGCACCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1163
GuideDesign90_ABE_NGC_20nt_3-9_008_-31946042_spCas9	mAsmCsmAsAUCUGUGUUCUGGCACCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1164
GuideDesign90_ABE_NGC_20nt_3-12_020_-31946042_spCas9	mAsmCsmAsAUCUGUGUUCUGGCACCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1165
GuideDesign90_CBE_NGC_20nt_4-9_009_-31946042_spCas9	mAsmCsmAsAUCUGUGUUCUGGCACCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1166
GuideDesign90_ABE_NG_20nt_3-9_027_-31946043_spCas9	mAsmCsmAsAUCUGUGUUCUGGCACCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1167
GuideDesign90_CBE_NG_20nt_4-9_028_-31946043_spCas9	mAsmCsmAsAUCUGUGUUCUGGCACCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1168
GuideDesign90_ABE_NRN_20nt_3-9_021_-31946042_spCas9	mAsmCsmAsAUCUGUGUUCUGGCACCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1169
GuideDesign90_CBE_NRN_20nt_3-9_022_-31946042_spCas9	mAsmCsmAsAUCUGUGUUCUGGCACCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1170
GuideDesign90_MBE_NRN_20nt_3-9_023_-31946042_spCas9	mAsmCsmAsAUCUGUGUUCUGGCACCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1171
GuideDesign90_ABE_NGG_20nt_3-12_018_+31946054_spCas9	mAsmCsmAsCAGAUUGUAUAAAAGGCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1172
GuideDesign90_ABE_NGG_20nt_13-16_032_+31946054_SpCas9	mAsmCsmAsCAGAUUGUAUAAAAGGCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1173
GuideDesign90_CBE_NGG_20nt_4-9_003_+31946054_spCas9	mAsmCsmAsCAGAUUGUAUAAAAGGCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1174
GuideDesign90_CBE_NGG_20nt_3-9_029_+31946054_spCas9	mAsmCsmAsCAGAUUGUAUAAAAGGCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1175
GuideDesign90_CBE_NGG_20nt_3-16_033_+31946054_SpCas9	mAsmCsmAsCAGAUUGUAUAAAAGGCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1176
GuideDesign90_ABE_NG_20nt_3-9_027_+31946054_spCas9	mAsmCsmAsCAGAUUGUAUAAAAGGCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1177
GuideDesign90_CBE_NG_20nt_4-9_028_+31946054_spCas9	mAsmCsmAsCAGAUUGUAUAAAAGGCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1178

Guide polynucleotide name	Guide polynucleotide sequence	SEQ ID NO
GuideDesign90_ABE_NRN_20nt_3-9_021 + 31946054_spCas9	mAsmCsmAsCAGAUUGUAUAAAAGGCGUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1179
GuideDesign90_CBE_NRN_20nt_3-9_022 + 31946054_spCas9	mAsmCsmAsCAGAUUGUAUAAAAGGCGUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1180
GuideDesign90_MBE_NRN_20nt_3-9_023 + 31946054_spCas9	mAsmCsmAsCAGAUUGUAUAAAAGGCGUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1181
GuideDesign90_ABE_NGG_20nt_3-12_018 + 31946056_spCas9	mAsmCsmAsGAUUGUAUAAAAGGCUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1182
GuideDesign90_ABE_NGG_20nt_13-16_032 + 31946056_SpCas9	mAsmCsmAsGAUUGUAUAAAAGGCUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1183
GuideDesign90_CBE_NGG_20nt_4-9_003 + 31946056_spCas9	mAsmCsmAsGAUUGUAUAAAAGGCUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1184
GuideDesign90_CBE_NGG_20nt_3-9_029 + 31946056_spCas9	mAsmCsmAsGAUUGUAUAAAAGGCUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1185
GuideDesign90_CBE_NGG_20nt_3-16_033 + 31946056_SpCas9	mAsmCsmAsGAUUGUAUAAAAGGCUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1186
GuideDesign90_ABE_NG_20nt_3-9_027 + 31946056_spCas9	mAsmCsmAsGAUUGUAUAAAAGGCUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1187
GuideDesign90_CBE_NG_20nt_4-9_028 + 31946056_spCas9	mAsmCsmAsGAUUGUAUAAAAGGCUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1188
GuideDesign90_ABE_NRN_20nt_3-9_021 + 31946056_spCas9	mAsmCsmAsGAUUGUAUAAAAGGCUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1189
GuideDesign90_CBE_NRN_20nt_3-9_022 + 31946056_spCas9	mAsmCsmAsGAUUGUAUAAAAGGCUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1190
GuideDesign90_MBE_NRN_20nt_3-9_023 + 31946056_spCas9	mAsmCsmAsGAUUGUAUAAAAGGCUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1191
GuideDesign90_ABE_NGC_20nt_3-12_020 + 31946051_spCas9	mAsmGsmAsACACAGAUUGUAUAAAAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1192
GuideDesign90_CBE_NGC_20nt_4-9_009 + 31946051_spCas9	mAsmGsmAsACACAGAUUGUAUAAAAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1193
GuideDesign90_ABE_NG_20nt_3-9_027 + 31946051_spCas9	mAsmGsmAsACACAGAUUGUAUAAAAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1194

Guide polynucleotide name	Guide polynucleotide sequence	SEQ ID NO
GuideDesign90_CBE_NG_20nt_4-9_028 + 31946051_spCas9	mAsmGsmAsACACAGAUUGUAUAAAAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1195
GuideDesign90_ABE_NRN_20nt_3-9_021 + 31946051_spCas9	mAsmGsmAsACACAGAUUGUAUAAAAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1196
GuideDesign90_CBE_NRN_20nt_3-9_022 + 31946051_spCas9	mAsmGsmAsACACAGAUUGUAUAAAAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1197
GuideDesign90_MBE_NRN_20nt_3-9_023 + 31946051_spCas9	mAsmGsmAsACACAGAUUGUAUAAAAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1198
GuideDesign90_ABE_NRCH_20nt_3-9_024 + 31946051_spCas9	mAsmGsmAsACACAGAUUGUAUAAAAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1199
GuideDesign90_CBE_NRCH_20nt_3-9_030 + 31946051_spCas9	mAsmGsmAsACACAGAUUGUAUAAAAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1200
GuideDesign90_ABE_NGC_20nt_3-9_008 + 31946058_spCas9	mAsmGsmAsUUGUAUAAAAGGCUUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1201
GuideDesign90_ABE_NGC_20nt_3-12_020 + 31946058_spCas9	mAsmGsmAsUUGUAUAAAAGGCUUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1202
GuideDesign90_CBE_NGC_20nt_4-9_009 + 31946058_spCas9	mAsmGsmAsUUGUAUAAAAGGCUUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1203
GuideDesign90_ABE_NG_20nt_3-9_027 + 31946058_spCas9	mAsmGsmAsUUGUAUAAAAGGCUUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1204
GuideDesign90_CBE_NG_20nt_4-9_028 + 31946058_spCas9	mAsmGsmAsUUGUAUAAAAGGCUUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1205
GuideDesign90_ABE_NRN_20nt_3-9_021 + 31946058_spCas9	mAsmGsmAsUUGUAUAAAAGGCUUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1206
GuideDesign90_CBE_NRN_20nt_3-9_022 + 31946058_spCas9	mAsmGsmAsUUGUAUAAAAGGCUUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1207
GuideDesign90_MBE_NRN_20nt_3-9_023 + 31946058_spCas9	mAsmGsmAsUUGUAUAAAAGGCUUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1208
GuideDesign90_ABE_NRCH_20nt_3-9_024 + 31946058_spCas9	mAsmGsmAsUUGUAUAAAAGGCUUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1209
GuideDesign90_CBE_NRCH_20nt_3-9_030 + 31946058_spCas9	mAsmGsmAsUUGUAUAAAAGGCUUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1210
GuideDesign90_CBE_NNRR_21nt_3-12_015 + 31946058_saCas9	mAsmGsmAsUUGUAUAAAAGGCUUGGGUUUUAGUACUCUG UAAUGAAAAUUACAGAAUCUACUAAAACAAGGCAAAUGCC GUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU	1211

Guide polynucleotide name	Guide polynucleotide sequence	SEQ ID NO
GuideDesign90_ABE_NGG_20nt_3-12_018 + 31946065_spCas9	mAsmUsmAsAAAAGGCUGGGGGCUGGUGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1212
GuideDesign90_CBE_NGG_20nt_4-9_003 + 31946065_spCas9	mAsmUsmAsAAAAGGCUGGGGGCUGGUGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1213
GuideDesign90_CBE_NGG_20nt_3-9_029 + 31946065_spCas9	mAsmUsmAsAAAAGGCUGGGGGCUGGUGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1214
GuideDesign90_CBE_NGG_20nt_3-16_033 + 31946065_SpCas9	mAsmUsmAsAAAAGGCUGGGGGCUGGUGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1215
GuideDesign90_ABE_NG_20nt_3-9_027 + 31946065_spCas9	mAsmUsmAsAAAAGGCUGGGGGCUGGUGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1216
GuideDesign90_CBE_NG_20nt_4-9_028 + 31946065_spCas9	mAsmUsmAsAAAAGGCUGGGGGCUGGUGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1217
GuideDesign90_ABE_NRN_20nt_3-9_021 + 31946065_spCas9	mAsmUsmAsAAAAGGCUGGGGGCUGGUGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1218
GuideDesign90_CBE_NRN_20nt_3-9_022 + 31946065_spCas9	mAsmUsmAsAAAAGGCUGGGGGCUGGUGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1219
GuideDesign90_MBE_NRN_20nt_3-9_023 + 31946065_spCas9	mAsmUsmAsAAAAGGCUGGGGGCUGGUGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1220
GuideDesign90_ABE_NGC_20nt_3-12_020 - 31946039_spCas9	mAsmUsmCsUGUGUUCUGGCACCGUGCGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1221
GuideDesign90_CBE_NGC_20nt_4-9_009 - 31946039_spCas9	mAsmUsmCsUGUGUUCUGGCACCGUGCGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1222
GuideDesign90_ABE_NG_20nt_3-9_027 - 31946040_spCas9	mAsmUsmCsUGUGUUCUGGCACCGUGCGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1223
GuideDesign90_CBE_NG_20nt_4-9_028 - 31946040_spCas9	mAsmUsmCsUGUGUUCUGGCACCGUGCGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1224
GuideDesign90_ABE_NRN_20nt_3-9_021 - 31946039_spCas9	mAsmUsmCsUGUGUUCUGGCACCGUGCGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1225
GuideDesign90_CBE_NRN_20nt_3-9_022 - 31946039_spCas9	mAsmUsmCsUGUGUUCUGGCACCGUGCGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1226
GuideDesign90_MBE_NRN_20nt_3-9_023 - 31946039_spCas9	mAsmUsmCsUGUGUUCUGGCACCGUGCGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1227

Guide polynucleotide name	Guide polynucleotide sequence	SEQ ID NO
GuideDesign90_ABE_NRCH_20nt_3-9_024_-31946038_spCas9	mAsmUsmCsUGUGUUCUGGCACCUGCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1228
GuideDesign90_CBE_NRCH_20nt_3-9_030_-31946038_spCas9	mAsmUsmCsUGUGUUCUGGCACCUGCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1229
GuideDesign90_ABE_NGG_20nt_3-12_018_+31946055_spCas9	mCsmAsmCsAGAUUGUAUAAAAGGCUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1230
GuideDesign90_ABE_NGG_20nt_13-16_032_+_31946055_SpCas9	mCsmAsmCsAGAUUGUAUAAAAGGCUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1231
GuideDesign90_CBE_NGG_20nt_4-9_003_+31946055_spCas9	mCsmAsmCsAGAUUGUAUAAAAGGCUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1232
GuideDesign90_CBE_NGG_20nt_3-9_029_+31946055_spCas9	mCsmAsmCsAGAUUGUAUAAAAGGCUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1233
GuideDesign90_CBE_NGG_20nt_3-16_033_+_31946055_SpCas9	mCsmAsmCsAGAUUGUAUAAAAGGCUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1234
GuideDesign90_ABE_NG_20nt_3-9_027_+31946055_spCas9	mCsmAsmCsAGAUUGUAUAAAAGGCUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1235
GuideDesign90_CBE_NG_20nt_4-9_028_+31946055_spCas9	mCsmAsmCsAGAUUGUAUAAAAGGCUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1236
GuideDesign90_ABE_NRN_20nt_3-9_021_+31946055_spCas9	mCsmAsmCsAGAUUGUAUAAAAGGCUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1237
GuideDesign90_CBE_NRN_20nt_3-9_022_+31946055_spCas9	mCsmAsmCsAGAUUGUAUAAAAGGCUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1238
GuideDesign90_MBE_NRN_20nt_3-9_023_+31946055_spCas9	mCsmAsmCsAGAUUGUAUAAAAGGCUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1239
GuideDesign90_ABE_NGG_20nt_3-12_018_+31946050_spCas9	mCsmAsmGsAACACAGAUUGUAUAAAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1240
GuideDesign90_ABE_NGG_20nt_13-16_032_+_31946050_SpCas9	mCsmAsmGsAACACAGAUUGUAUAAAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1241
GuideDesign90_CBE_NGG_20nt_4-9_003_+31946050_spCas9	mCsmAsmGsAACACAGAUUGUAUAAAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1242
GuideDesign90_CBE_NGG_20nt_3-9_029_+31946050_spCas9	mCsmAsmGsAACACAGAUUGUAUAAAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1243

Guide polynucleotide name	Guide polynucleotide sequence	SEQ ID NO
GuideDesign90_CBE_NGG_20nt_3-16_033+_31946050_SpCas9	mCsmAsmGsAACACAGAUUGUAUAAAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1244
GuideDesign90_ABE_NG_20nt_3-9_027 + 31946050 spCas9	mCsmAsmGsAACACAGAUUGUAUAAAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1245
GuideDesign90_CBE_NG_20nt_4-9_028 + 31946050 spCas9	mCsmAsmGsAACACAGAUUGUAUAAAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1246
GuideDesign90_ABE_NRN_20nt_3-9_021 + 31946050 spCas9	mCsmAsmGsAACACAGAUUGUAUAAAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1247
GuideDesign90_CBE_NRN_20nt_3-9_022 + 31946050 spCas9	mCsmAsmGsAACACAGAUUGUAUAAAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1248
GuideDesign90_MBE_NRN_20nt_3-9_023 + 31946050 spCas9	mCsmAsmGsAACACAGAUUGUAUAAAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1249
GuideDesign90_CBE_NRRH_20nt_3-9_031 + 31946050 spCas9	mCsmAsmGsAACACAGAUUGUAUAAAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1250
GuideDesign90_ABE_NGG_20nt_3-12_018 + 31946057 spCas9	mCsmAsmGsAUUGUAUAAAAGGCUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1251
GuideDesign90_ABE_NGG_20nt_13-16_032+_31946057_SpCas9	mCsmAsmGsAUUGUAUAAAAGGCUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1252
GuideDesign90_CBE_NGG_20nt_4-9_003 + 31946057 spCas9	mCsmAsmGsAUUGUAUAAAAGGCUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1253
GuideDesign90_CBE_NGG_20nt_3-9_029 + 31946057 spCas9	mCsmAsmGsAUUGUAUAAAAGGCUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1254
GuideDesign90_CBE_NGG_20nt_3-16_033+_31946057_SpCas9	mCsmAsmGsAUUGUAUAAAAGGCUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1255
GuideDesign90_ABE_NG_20nt_3-9_027 + 31946057 spCas9	mCsmAsmGsAUUGUAUAAAAGGCUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1256
GuideDesign90_CBE_NG_20nt_4-9_028 + 31946057 spCas9	mCsmAsmGsAUUGUAUAAAAGGCUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1257
GuideDesign90_ABE_NRN_20nt_3-9_021 + 31946057 spCas9	mCsmAsmGsAUUGUAUAAAAGGCUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1258
GuideDesign90_CBE_NRN_20nt_3-9_022 + 31946057 spCas9	mCsmAsmGsAUUGUAUAAAAGGCUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1259

Guide polynucleotide name	Guide polynucleotide sequence	SEQ ID NO
GuideDesign90_MBE_NRN_20nt_3-9_023 + 31946057_spCas9	mCsmAsmGsAUUGUAUAAAAGGCUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1260
GuideDesign90_CBE_NRRH_20nt_3-9_031 + 31946057_spCas9	mCsmAsmGsAUUGUAUAAAAGGCUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1261
GuideDesign90_ABE_NRN_20nt_3-9_021 - 31946060_spCas9	mCsmAsmGsCCCCAGCCUUUUUAUACGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1262
GuideDesign90_CBE_NRN_20nt_3-9_022 - 31946060_spCas9	mCsmAsmGsCCCCAGCCUUUUUAUACGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1263
GuideDesign90_MBE_NRN_20nt_3-9_023 - 31946060_spCas9	mCsmAsmGsCCCCAGCCUUUUUAUACGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1264
GuideDesign90_ABE_NRTH_20nt_3-9_025 - 31946059_spCas9	mCsmAsmGsCCCCAGCCUUUUUAUACGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1265
GuideDesign90_CBE_NRTH_20nt_4-9_026 - 31946059_spCas9	mCsmAsmGsCCCCAGCCUUUUUAUACGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1266
GuideDesign90_CBE_NNR RT_21nt_3-12_015 - 31946060_saCas9	mCsmCsmAsCCAGCCCCAGCCUUUUAGUUUUAGUACUCUG UAAUGAAAAUUACAGAAUCUACUAAAAACAAGGCAAAUGCC GUGUUUAUCUCGUAACUUGUUGGCGAGAUsmUsmUsmU	1267
GuideDesign90_ABE_NRN_20nt_3-9_021 - 31946061_spCas9	mCsmCsmAsGCCCCAGCCUUUUUAUAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1268
GuideDesign90_CBE_NRN_20nt_3-9_022 - 31946061_spCas9	mCsmCsmAsGCCCCAGCCUUUUUAUAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1269
GuideDesign90_MBE_NRN_20nt_3-9_023 - 31946061_spCas9	mCsmCsmAsGCCCCAGCCUUUUUAUAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1270
GuideDesign90_CBE_NRRH_20nt_3-9_031 - 31946060_spCas9	mCsmCsmAsGCCCCAGCCUUUUUAUAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1271
GuideDesign90_ABE_NG_20nt_3-9_027 - 31946055_spCas9	mCsmCsmAsGCCUUUUUAUACAAUCUGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1272
GuideDesign90_CBE_NG_20nt_4-9_028 - 31946055_spCas9	mCsmCsmAsGCCUUUUUAUACAAUCUGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1273
GuideDesign90_ABE_NRN_20nt_3-9_021 - 31946054_spCas9	mCsmCsmAsGCCUUUUUAUACAAUCUGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1274
GuideDesign90_CBE_NRN_20nt_3-9_022 - 31946054_spCas9	mCsmCsmAsGCCUUUUUAUACAAUCUGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1275
GuideDesign90_MBE_NRN_20nt_3-9_023 - 31946054_spCas9	mCsmCsmAsGCCUUUUUAUACAAUCUGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1276

Guide polynucleotide name	Guide polynucleotide sequence	SEQ ID NO
GuideDesign90_ABE_NRTH_20nt_3-9_025_-31946053_spCas9	mCsmCsmAsGCCUUUUUAUACAAUCUGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1277
GuideDesign90_CBE_NRTH_20nt_4-9_026_-31946053_spCas9	mCsmCsmAsGCCUUUUUAUACAAUCUGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1278
GuideDesign90_ABE_NG_20nt_3-9_027_-31946057_spCas9	mCsmCsmCsCAGCCUUUUUAUACAAUCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1279
GuideDesign90_CBE_NG_20nt_4-9_028_-31946057_spCas9	mCsmCsmCsCAGCCUUUUUAUACAAUCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1280
GuideDesign90_ABE_NRN_20nt_3-9_021_-31946056_spCas9	mCsmCsmCsCAGCCUUUUUAUACAAUCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1281
GuideDesign90_CBE_NRN_20nt_3-9_022_-31946056_spCas9	mCsmCsmCsCAGCCUUUUUAUACAAUCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1282
GuideDesign90_MBE_NRN_20nt_3-9_023_-31946056_spCas9	mCsmCsmCsCAGCCUUUUUAUACAAUCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1283
GuideDesign90_ABE_NGG_20nt_3-9_002 + 31946073_spCas9	mCsmUsmGsGGGGCUGGUGGGGAGCAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1284
GuideDesign90_ABE_NGG_20nt_3-12_018 + 31946073_spCas9	mCsmUsmGsGGGGCUGGUGGGGAGCAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1285
GuideDesign90_CBE_NGG_20nt_4-9_003 + 31946073_spCas9	mCsmUsmGsGGGGCUGGUGGGGAGCAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1286
GuideDesign90_CBE_NGG_20nt_3-9_029 + 31946073_spCas9	mCsmUsmGsGGGGCUGGUGGGGAGCAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1287
GuideDesign90_CBE_NGG_20nt_3-16_033 + 31946073_SpCas9	mCsmUsmGsGGGGCUGGUGGGGAGCAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1288
GuideDesign90_ABE_NG_20nt_3-9_027 + 31946073_spCas9	mCsmUsmGsGGGGCUGGUGGGGAGCAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1289
GuideDesign90_CBE_NG_20nt_4-9_028 + 31946073_spCas9	mCsmUsmGsGGGGCUGGUGGGGAGCAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1290
GuideDesign90_ABE_NRN_20nt_3-9_021 + 31946073_spCas9	mCsmUsmGsGGGGCUGGUGGGGAGCAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1291
GuideDesign90_CBE_NRN_20nt_3-9_022 + 31946073_spCas9	mCsmUsmGsGGGGCUGGUGGGGAGCAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1292

Guide polynucleotide name	Guide polynucleotide sequence	SEQ ID NO
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GuideDesign90_ABE_NGG_20nt_3-12_018 - 31946049_spCas9	mCsmUsmUsUUAUACAAUCUGUGUUCGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1294
GuideDesign90_ABE_NGG_20nt_13-16_032 - 31946049_SpCas9	mCsmUsmUsUUAUACAAUCUGUGUUCGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1295
GuideDesign90_CBE_NGG_20nt_4-9_003 - 31946049_spCas9	mCsmUsmUsUUAUACAAUCUGUGUUCGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1296
GuideDesign90_CBE_NGG_20nt_3-9_029 - 31946049_spCas9	mCsmUsmUsUUAUACAAUCUGUGUUCGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1297
GuideDesign90_CBE_NGG_20nt_3-16_033 - 31946049_SpCas9	mCsmUsmUsUUAUACAAUCUGUGUUCGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1298
GuideDesign90_ABE_NG_20nt_3-9_027 - 31946050_spCas9	mCsmUsmUsUUAUACAAUCUGUGUUCGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1299
GuideDesign90_CBE_NG_20nt_4-9_028 - 31946050_spCas9	mCsmUsmUsUUAUACAAUCUGUGUUCGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1300
GuideDesign90_ABE_NRN_20nt_3-9_021 - 31946049_spCas9	mCsmUsmUsUUAUACAAUCUGUGUUCGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1301
GuideDesign90_CBE_NRN_20nt_3-9_022 - 31946049_spCas9	mCsmUsmUsUUAUACAAUCUGUGUUCGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1302
GuideDesign90_MBE_NRN_20nt_3-9_023 - 31946049_spCas9	mCsmUsmUsUUAUACAAUCUGUGUUCGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1303
GuideDesign90_CBE_NRRH_20nt_3-9_031 - 31946048_spCas9	mCsmUsmUsUUAUACAAUCUGUGUUCGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1304
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GuideDesign90_ABE_NGG_20nt_3-12_018 + 31946072_spCas9	mGsmCsmUsGGGGGCGUGGGGAGCGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1306
GuideDesign90_CBE_NGG_20nt_4-9_003 + 31946072_spCas9	mGsmCsmUsGGGGGCGUGGGGAGCGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1307
GuideDesign90_CBE_NGG_20nt_3-9_029 + 31946072_spCas9	mGsmCsmUsGGGGGCGUGGGGAGCGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1308
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Guide polynucleotide name	Guide polynucleotide sequence	SEQ ID NO
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GuideDesign90_CBE_NG_20nt_4-9_028 + 31946072_spCas9	mGsmCsmUsGGGGGCUGGUGGGGAGCGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1311
GuideDesign90_ABE_NRN_20nt_3-9_021 + 31946072_spCas9	mGsmCsmUsGGGGGCUGGUGGGGAGCGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1312
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GuideDesign90_MBE_NRN_20nt_3-9_023 + 31946071_spCas9	mGsmGsmCsUGGGGGCUGGUGGGGAGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1317
GuideDesign90_ABE_NGG_20nt_3-12_018 + 31946066_spCas9	mUsmAsmAsAAGGCUGGGGGCUGGUGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1318
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GuideDesign90_CBE_NG_20nt_4-9_028 + 31946066_spCas9	mUsmAsmAsAAGGCUGGGGGCUGGUGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1323
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Guide polynucleotide name	Guide polynucleotide sequence	SEQ ID NO
GuideDesign90_MBE_NRN_20nt_3-9_023 + 31946066_spCas9	mUsmAsmAsAAGGCUGGGGGCUGGUGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1326
GuideDesign90_CBE_NRRH_20nt_3-9_031 + 31946066_spCas9	mUsmAsmAsAAGGCUGGGGGCUGGUGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1327
GuideDesign90_ABE_NGG_20nt_3-12_018 + 31946064_spCas9	mUsmAsmUsAAAAAGGCUGGGGGCUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1328
GuideDesign90_ABE_NGG_20nt_13-16_032+_31946064_SpCas9	mUsmAsmUsAAAAAGGCUGGGGGCUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1329
GuideDesign90_CBE_NGG_20nt_4-9_003 + 31946064_spCas9	mUsmAsmUsAAAAAGGCUGGGGGCUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1330
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GuideDesign90_CBE_NGG_20nt_3-16_033+_31946064_SpCas9	mUsmAsmUsAAAAAGGCUGGGGGCUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1332
GuideDesign90_ABE_NG_20nt_3-9_027 + 31946064_spCas9	mUsmAsmUsAAAAAGGCUGGGGGCUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1333
GuideDesign90_CBE_NG_20nt_4-9_028 + 31946064_spCas9	mUsmAsmUsAAAAAGGCUGGGGGCUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1334
GuideDesign90_ABE_NRN_20nt_3-9_021 + 31946064_spCas9	mUsmAsmUsAAAAAGGCUGGGGGCUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1335
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GuideDesign90_ABE_NGG_20nt_3-9_002 + 31946074_spCas9	mUsmGsmGsGGGCUGGUGGGGAGCAGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1340

Guide polynucleotide name	Guide polynucleotide sequence	SEQ ID NO
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GuideDesign90_CBE_NGG_20nt_3-9_029 + 31946074_spCas9	mUsmGsmGsGGGCUGGUGGGGAGCAGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1342
GuideDesign90_CBE_NGG_20nt_3-16_033 + 31946074_SpCas9	mUsmGsmGsGGGCUGGUGGGGAGCAGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1343
GuideDesign90_ABE_NG_20nt_3-9_027 + 31946074_spCas9	mUsmGsmGsGGGCUGGUGGGGAGCAGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1344
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GuideDesign90_CBE_NRN_20nt_3-9_022 + 31946074_spCas9	mUsmGsmGsGGGCUGGUGGGGAGCAGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1346
GuideDesign90_MBE_NRN_20nt_3-9_023 + 31946074_spCas9	mUsmGsmGsGGGCUGGUGGGGAGCAGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1347
GuideDesign90_ABE_NG_20nt_3-9_027 + 31946062_spCas9	mUsmGsmUsAUAAAAGGCUGGGGGCUGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1348
GuideDesign90_CBE_NG_20nt_4-9_028 + 31946062_spCas9	mUsmGsmUsAUAAAAGGCUGGGGGCUGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1349
GuideDesign90_ABE_NRN_20nt_3-9_021 + 31946062_spCas9	mUsmGsmUsAUAAAAGGCUGGGGGCUGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1350
GuideDesign90_CBE_NRN_20nt_3-9_022 + 31946062_spCas9	mUsmGsmUsAUAAAAGGCUGGGGGCUGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1351
GuideDesign90_MBE_NRN_20nt_3-9_023 + 31946062_spCas9	mUsmGsmUsAUAAAAGGCUGGGGGCUGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1352
GuideDesign90_ABE_NRN_20nt_3-9_021 - 31946046_spCas9	mUsmUsmAsUACAAUCUGUGUUCUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1353
GuideDesign90_CBE_NRN_20nt_3-9_022 - 31946046_spCas9	mUsmUsmAsUACAAUCUGUGUUCUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1354
GuideDesign90_MBE_NRN_20nt_3-9_023 - 31946046_spCas9	mUsmUsmAsUACAAUCUGUGUUCUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1355
GuideDesign90_ABE_NRCH_20nt_3-9_024 - 31946045_spCas9	mUsmUsmAsUACAAUCUGUGUUCUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1356

Guide polynucleotide name	Guide polynucleotide sequence	SEQ ID NO
GuideDesign90_CBE_NRCH_20nt_3-9_030_-31946045_spCas9	mUsmUsmAsUACAAUCUGUGUUCUGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1357
GuideDesign90_ABE_NGG_20nt_3-9_002 + 31946061_spCas9	mUsmUsmGsUAUAAAAGGCUGGGGGCGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1358
GuideDesign90_ABE_NGG_20nt_3-12_018 + 31946061_spCas9	mUsmUsmGsUAUAAAAGGCUGGGGGCGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1359
GuideDesign90_ABE_NGG_20nt_13-16_032_+_31946061_SpCas9	mUsmUsmGsUAUAAAAGGCUGGGGGCGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1360
GuideDesign90_CBE_NGG_20nt_4-9_003 + 31946061_spCas9	mUsmUsmGsUAUAAAAGGCUGGGGGCGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1361
GuideDesign90_CBE_NGG_20nt_3-9_029 + 31946061_spCas9	mUsmUsmGsUAUAAAAGGCUGGGGGCGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1362
GuideDesign90_CBE_NGG_20nt_3-16_033_+_31946061_SpCas9	mUsmUsmGsUAUAAAAGGCUGGGGGCGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1363
GuideDesign90_ABE_NG_20nt_3-9_027 + 31946061_spCas9	mUsmUsmGsUAUAAAAGGCUGGGGGCGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1364
GuideDesign90_CBE_NG_20nt_4-9_028 + 31946061_spCas9	mUsmUsmGsUAUAAAAGGCUGGGGGCGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1365
GuideDesign90_ABE_NRN_20nt_3-9_021 + 31946061_spCas9	mUsmUsmGsUAUAAAAGGCUGGGGGCGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1366
GuideDesign90_CBE_NRN_20nt_3-9_022 + 31946061_spCas9	mUsmUsmGsUAUAAAAGGCUGGGGGCGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1367
GuideDesign90_MBE_NRN_20nt_3-9_023 + 31946061_spCas9	mUsmUsmGsUAUAAAAGGCUGGGGGCGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1368
GuideDesign90_CBE_NRRH_20nt_3-9_031 + 31946061_spCas9	mUsmUsmGsUAUAAAAGGCUGGGGGCGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1369
GuideDesign90_ABE_NGC_20nt_3-9_008_-31946048_spCas9	mUsmUsmUsUAUACAAUCUGUGUUCUGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1370
GuideDesign90_ABE_NGC_20nt_3-12_020_-31946048_spCas9	mUsmUsmUsUAUACAAUCUGUGUUCUGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1371
GuideDesign90_CBE_NGC_20nt_4-9_009_-31946048_spCas9	mUsmUsmUsUAUACAAUCUGUGUUCUGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1372

Guide polynucleotide name	Guide polynucleotide sequence	SEQ ID NO
GuideDesign90_ABE_NG_2 0nt_3-9_027_- 31946049_spCas9	mUsmUsmUsUAUACAAUCUGUGUUCUGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1373
GuideDesign90_CBE_NG_2 0nt_4-9_028_- 31946049_spCas9	mUsmUsmUsUAUACAAUCUGUGUUCUGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1374
GuideDesign90_ABE_NRN_ 20nt_3-9_021_- 31946048_spCas9	mUsmUsmUsUAUACAAUCUGUGUUCUGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1375
GuideDesign90_CBE_NRN_ 20nt_3-9_022_- 31946048_spCas9	mUsmUsmUsUAUACAAUCUGUGUUCUGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1376
GuideDesign90_MBE_NRN_ 20nt_3-9_023_- 31946048_spCas9	mUsmUsmUsUAUACAAUCUGUGUUCUGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1377
GuideDesign90_ABE_NRCH_ 20nt_3-9_024_- 31946047_spCas9	mUsmUsmUsUAUACAAUCUGUGUUCUGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1378
GuideDesign90_CBE_NRCH_ 20nt_3-9_030_- 31946047_spCas9	mUsmUsmUsUAUACAAUCUGUGUUCUGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1379
GuideDesign90_ABE_NRN_ 20nt_3- 9_021 + 31946215_spCas9	mAsmAsmCsGCCAUGGGGAGCAAUCUGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1380
GuideDesign90_MBE_NRN_ 20nt_3- 9_023 + 31946215_spCas9	mAsmAsmCsGCCAUGGGGAGCAAUCUGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1381
GuideDesign90_ABE_NGC_ 20nt_3- 9_008 + 31946216_spCas9	mAsmCsmGsCCAUGGGGAGCAAUCUGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1382
GuideDesign90_ABE_NGC_ 20nt_3- 12_020 + 31946216_spCas9	mAsmCsmGsCCAUGGGGAGCAAUCUGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1383
GuideDesign90_ABE_NG_2 0nt_3- 9_027 + 31946216_spCas9	mAsmCsmGsCCAUGGGGAGCAAUCUGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1384
GuideDesign90_ABE_NRN_ 20nt_3- 9_021 + 31946216_spCas9	mAsmCsmGsCCAUGGGGAGCAAUCUGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1385
GuideDesign90_MBE_NRN_ 20nt_3- 9_023 + 31946216_spCas9	mAsmCsmGsCCAUGGGGAGCAAUCUGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1386
GuideDesign90_ABE_NRCH_ 20nt_3- 9_024 + 31946216_spCas9	mAsmCsmGsCCAUGGGGAGCAAUCUGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1387
GuideDesign90_CBE_NGA_ 20nt_3-16_035_- 31946212_spCas9	mAsmGsmAsUUGCUCCCCAUGGCGUUGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1388
GuideDesign90_ABE_VTTN_ 22nt_5- 9_017 + 31946210_cas12b	mGsmUsmUsCUGUCUUUUGGUCAGGACAACCGUCUAGCUAU AAGUGCUGCAGGGUGUGAGAAACUCCUAUUGCUGGACGAUG	1389

Guide polynucleotide name	Guide polynucleotide sequence	SEQ ID NO
	UCUCUUACGAGGCAUUAGCACCAACGCCAUGGGGAGCAAUs mCsmUsmC	
GuideDesign90_ABE_NG_2 0nt_3-9_027_- 31946203 spCas9	mCsmCsmAsUGGCGUUGGAAGGCAGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1390
GuideDesign90_ABE_NRN_ 20nt_3-9_021_- 31946202 spCas9	mCsmCsmAsUGGCGUUGGAAGGCAGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1391
GuideDesign90_MBE_NRN_ 20nt_3-9_023_- 31946202 spCas9	mCsmCsmAsUGGCGUUGGAAGGCAGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1392
GuideDesign90_ABE_NGA_ 20nt_3-12_019_- 31946202 spCas9	mCsmCsmAsUGGCGUUGGAAGGCAGGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1393
GuideDesign90_ABE_NRN_ 20nt_3-9_021_- 31946203 spCas9	mCsmCsmCsAUGGCGUUGGAAGGCAGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1394
GuideDesign90_CBE_NRN_ 20nt_3-9_022_- 31946203 spCas9	mCsmCsmCsAUGGCGUUGGAAGGCAGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1395
GuideDesign90_MBE_NRN_ 20nt_3-9_023_- 31946203 spCas9	mCsmCsmCsAUGGCGUUGGAAGGCAGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1396
GuideDesign90_CBE_NRRH_ 20nt_3-9_031_- 31946202 spCas9	mCsmCsmCsAUGGCGUUGGAAGGCAGGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1397
GuideDesign90_CBE_NGA_ 20nt_3-16_035_- 31946204 spCas9	mCsmCsmCsCAUGGCGUUGGAAGGCAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1398
GuideDesign90_ABE_NG_2 0nt_3-9_027_- 31946205 spCas9	mCsmCsmCsCAUGGCGUUGGAAGGCAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1399
GuideDesign90_CBE_NG_2 0nt_4-9_028_- 31946205 spCas9	mCsmCsmCsCAUGGCGUUGGAAGGCAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1400
GuideDesign90_ABE_NRN_ 20nt_3-9_021_- 31946204 spCas9	mCsmCsmCsCAUGGCGUUGGAAGGCAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1401
GuideDesign90_CBE_NRN_ 20nt_3-9_022_- 31946204 spCas9	mCsmCsmCsCAUGGCGUUGGAAGGCAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1402
GuideDesign90_MBE_NRN_ 20nt_3-9_023_- 31946204 spCas9	mCsmCsmCsCAUGGCGUUGGAAGGCAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1403
GuideDesign90_ABE_NGA_ 20nt_3-12_019_- 31946204 spCas9	mCsmCsmCsCAUGGCGUUGGAAGGCAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1404
GuideDesign90_CBE_NGA_ 20nt_4-9_006_- 31946204 spCas9	mCsmCsmCsCAUGGCGUUGGAAGGCAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1405

Guide polynucleotide name	Guide polynucleotide sequence	SEQ ID NO
GuideDesign90_ABE_NRN_20nt_3-9_021_-31946206_spCas9	mCsmUsmCsCCCAUGGCGUUGGAAGGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1406
GuideDesign90_CBE_NRN_20nt_3-9_022_-31946206_spCas9	mCsmUsmCsCCCAUGGCGUUGGAAGGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1407
GuideDesign90_MBE_NRN_20nt_3-9_023_-31946206_spCas9	mCsmUsmCsCCCAUGGCGUUGGAAGGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1408
GuideDesign90_ABE_VTTN_22nt_5-9_017_-31946207_cas12b	mGsmUsmUsCUGUCUUUUGGUCAGGACAACCGUCUAGCUAUAAAGUCUGCAGGGUGUGAGAAACUCCUAUUGCUGGACGAUGUCUCUUACGAGGCAUAGCACCUCGCCAUGGCGUUGGAAGSmGsmCsmA	1409
GuideDesign90_CBE_NGG_20nt_3-16_033_-31946213_SpCas9	mGsmAsmGsAUUGCUCGCCAUGGCGUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1410
GuideDesign90_ABE_NGG_20nt_3-9_002_-31946205_spCas9	mUsmCsmCsCCAUGGCGUUGGAAGGCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1411
GuideDesign90_ABE_NG_20nt_3-9_027_-31946206_spCas9	mUsmCsmCsCCAUGGCGUUGGAAGGCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1412
GuideDesign90_CBE_NG_20nt_4-9_028_-31946206_spCas9	mUsmCsmCsCCAUGGCGUUGGAAGGCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1413
GuideDesign90_ABE_NGG_20nt_3-12_018_-31946205_spCas9	mUsmCsmCsCCAUGGCGUUGGAAGGCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1414
GuideDesign90_ABE_NRN_20nt_3-9_021_-31946205_spCas9	mUsmCsmCsCCAUGGCGUUGGAAGGCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1415
GuideDesign90_CBE_NRN_20nt_3-9_022_-31946205_spCas9	mUsmCsmCsCCAUGGCGUUGGAAGGCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1416
GuideDesign90_MBE_NRN_20nt_3-9_023_-31946205_spCas9	mUsmCsmCsCCAUGGCGUUGGAAGGCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1417
GuideDesign90_CBE_NRRH_20nt_3-9_031_-31946204_spCas9	mUsmCsmCsCCAUGGCGUUGGAAGGCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1418
GuideDesign90_CBE_NGG_20nt_4-9_003_-31946205_spCas9	mUsmCsmCsCCAUGGCGUUGGAAGGCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1419
GuideDesign90_CBE_NGG_20nt_3-9_029_-31946205_spCas9	mUsmCsmCsCCAUGGCGUUGGAAGGCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1420
GuideDesign90_CBE_NGG_20nt_3-16_033_-31946205_SpCas9	mUsmCsmCsCCAUGGCGUUGGAAGGCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1421

Guide polynucleotide name	Guide polynucleotide sequence	SEQ ID NO
GuideDesign90_ABE_NGC_20nt_3-12_020_-31946208_spCas9	mUsmGsmCsUCCCCAUGGCGUUGGAAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1422
GuideDesign90_CBE_NGC_20nt_4-9_009_-31946208_spCas9	mUsmGsmCsUCCCCAUGGCGUUGGAAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1423
GuideDesign90_ABE_NG_20nt_3-9_027_-31946209_spCas9	mUsmGsmCsUCCCCAUGGCGUUGGAAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1424
GuideDesign90_CBE_NG_20nt_4-9_028_-31946209_spCas9	mUsmGsmCsUCCCCAUGGCGUUGGAAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1425
GuideDesign90_ABE_NRN_20nt_3-9_021_-31946208_spCas9	mUsmGsmCsUCCCCAUGGCGUUGGAAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1426
GuideDesign90_CBE_NRN_20nt_3-9_022_-31946208_spCas9	mUsmGsmCsUCCCCAUGGCGUUGGAAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1427
GuideDesign90_MBE_NRN_20nt_3-9_023_-31946208_spCas9	mUsmGsmCsUCCCCAUGGCGUUGGAAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1428
GuideDesign90_ABE_NRCH_20nt_3-9_024_-31946207_spCas9	mUsmGsmCsUCCCCAUGGCGUUGGAAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1429
GuideDesign90_CBE_NRCH_20nt_3-9_030_-31946207_spCas9	mUsmGsmCsUCCCCAUGGCGUUGGAAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1430
GuideDesign90_CBE_NG_20nt_4-9_028_-31946210_spCas9	mUsmUsmGsCUCCCCAUGGCGUUGGAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1431
GuideDesign90_CBE_NRN_20nt_3-9_022_-31946209_spCas9	mUsmUsmGsCUCCCCAUGGCGUUGGAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1432
GuideDesign90_MBE_NRN_20nt_3-9_023_-31946209_spCas9	mUsmUsmGsCUCCCCAUGGCGUUGGAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1433
GuideDesign90_CBE_NRRH_20nt_3-9_031_-31946208_spCas9	mUsmUsmGsCUCCCCAUGGCGUUGGAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1434
GuideDesign90_CBE_NGG_20nt_4-9_003_-31946209_spCas9	mUsmUsmGsCUCCCCAUGGCGUUGGAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1435
GuideDesign90_CBE_NGG_20nt_3-9_029_-31946209_spCas9	mUsmUsmGsCUCCCCAUGGCGUUGGAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1436
GuideDesign90_CBE_NGG_20nt_3-16_033_-31946209_SpCas9	mUsmUsmGsCUCCCCAUGGCGUUGGAGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCmUsmUsmUsU	1437

Table 1E: Representative sequences for guide polynucleotides for use in guiding a base editor to alter a start codon or TATA box of a complement factor B polynucleotide using base editing.⁵

Guide polynucleotide name	Guide polynucleotide sequence	SEQ ID NO
gRNA3642	mCsmAsmGsAACACAGAUUGUAUAAAAGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCmUsmUsmUsU	1438
gRNA3643	mAsmCsmAsCAGAUUGUAUAAAAGGCGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCmUsmUsmUsU	1439
gRNA3644	mCsmAsmCsAGAUUGUAUAAAAGGCUGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCmUsmUsmUsU	1440
gRNA3645	mAsmCsmAsGAUUGUAUAAAAGGCUGGUUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCmUsmUsmUsU	1441
gRNA3646	mCsmAsmGsAUUGUAUAAAAGGCUGGGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCmUsmUsmUsU	1442
gRNA3647	mUsmAsmUsAAAAGGCUGGGGGCUGGGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCmUsmUsmUsU	1443
gRNA3648	mAsmUsmAsAAAGGCUGGGGGCUGGUGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCmUsmUsmUsU	1444
gRNA3649	mUsmAsmAsAAGGCUGGGGGCUGGUGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCmUsmUsmUsU	1445
gRNA3650	mCsmUsmUsUUAUACAAUCUGUGUUCGUUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCmUsmUsmUsU	1446
gRNA3651	mAsmAsmUsCUGUGUUCUGGCACCGUGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCmUsmUsmUsU	1447
gRNA3652	mAsmAsmAsAGGCUGGGGGCUGGUGGUUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCmUsmUsmUsU	1448
gRNA3653	mAsmGsmAsACACAGAUUGUAUAAAAGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCmUsmUsmUsU	1449
gRNA3654	mAsmUsmCsUGUGUUCUGGCACCGUGCGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCmUsmUsmUsU	1450
gRNA3655	mAsmGsmAsUUGUAUAAAAGGCUGGGGGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	1451
gRNA3656	mCsmCsmAsCCAGCCCCAGCCUUUUAGUUUUAGUACUCUGUAAUGAAAA UUACAGAAUCUACUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACU UGUUGGCGAGAUsmUsmUsmU	1452

⁵ “mN” indicates a 2'-OMe modification of the nucleotide “N”, and “Ns” indicates that the nucleotide “N” is linked to the following (i.e., 3') nucleotide by a phosphorothioate (PS).

Guide polynucleotide name	Guide polynucleotide sequence	SEQ ID NO
gRNA3657	mUsmGsmCsUCCCCAUGGCGUUGGAAGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCmUsmUsmUsU	1453
gRNA3658	mUsmUsmGsCUCCCCAUGGCGUUGGAGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCmUsmUsmUsU	1454
gRNA3659	mGsmAsmGsAUUGCUCUCCCCAUGGCGUGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCmUsmUsmUsU	1455
gRNA3660	mCsmCsmCsCAUGGCGUUGGAAGGCAGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCmUsmUsmUsU	1456
gRNA3661	mCsmCsmAsUGGCGUUGGAAGGCAGGGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCmUsmUsmUsU	1457
gRNA3662	mAsmGsmAsUUGCUCUCCCCAUGGCGUUGUUUUAGAGCUAGAAAUAGCAAGU UAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGU GCmUsmUsmUsU	1458

Table 1F: Representative sequences for guide polynucleotides for use in guiding a base editor to alter a complement factor B splice site.⁶

Target Site Name	Guide polynucleotide name	Nucleotide Modification on Scheme	Guide polynucleotide sequence	SEQ ID NO
TSBTx38 26	gRNA1 193	End Mods	mCsmCsmUsCAGAUGUCUAUGUGUUUGUUUUA GAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAG UCCGUUAUCAACUUGAAAAAGUGGCACCGAGU CGGUGCUsmUsmUsmU	1459
TSBTx38 26	gRNA2 210	HM01	mCsmCsmUsCAGAUGUCUAUGUGUUUGUUUUA GAmGmCmUmAmGmAmAmUmAmGmCAAGUUUA AAAUAAAGGCUAGUCCGUUAUCAmAmCmUmUmG mAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmG mUmCmGmGmUmGmCmUsmUsmUsmU	1460
TSBTx38 26	gRNA2 444	HM07	mCsmCsmUsmCmAmGmAmUmGmUCUAUGUGUU UmGUUUUAGmAmGmCmUmAmGmAmAmUmAm GmCmAmAGUUmAAmAAmUAmAmGmGmCmUmAG UmCmCGUUAmUmCAAmCmUmUmGmAmAmAmAm AmGmUmGmCmAmCmCmGmAmGmUmCmGmGmU mGmCmUsmUsmUsmU	1461
TSBTx38 26	gRNA2 445	NLS (bpsv40)	mCsmCsmUsCAGAUGUCUAUGUGUUUGUUUUA GAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAG UCCGUUAUCAACUUGAAAAAGUGGCACCGAGU CGGUGCmUsmUsmUsU - NHC6-CrossL-ac- CKRTADGSEFESPKKKRKV	1462 ; 1463

⁶ “mN” indicates a 2'-OMe modification of the nucleotide “N”, and “Ns” indicates that the nucleotide “N” is linked to the following (i.e., 3') nucleotide by a phosphorothioate (PS).

Target Site Name	Guide polynucleotide name	Nucleotide Modification Scheme	Guide polynucleotide sequence	SEQ ID NO
TSBTx38 26	gRNA2 446	Hairpin Extension (LONGEST T-OLD)	mCsmCsmUsCAGAUGUCUAUGUGUUUGUUUUA GAmGmCmCmGmGmCmGmGmAmAmAmCmGmCmC mGmGmCAAGUUAAAAUAAGGCUAGUCCGUUAU CAmAmCmUmUmGmAmAmAmAmAmGUGmGmCmA mCmCmGmAmGmUmCmGmGmUmGmCmUsmUsmU	1464
TSBTx38 26	gRNA3 335	LONGEST	mCsmCsmUsCAGAUGUCUAUGUGUUUGUUUUA GAmGmCmCmGmGmCmGmGmAmAmAmCmGmCmC mGmGmCAAGUUAAAAUAAGGCUAGUCCGUUAU CAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmC mAmCmCmGmAmGmUmCmGmGmUmGmCmUsmUs mUsmU	1465
TSBTx38 26	gRNA3 336	LONGEST +NLS	mCsmCsmUsCAGAUGUCUAUGUGUUUGUUUUA GAmGmCmCmGmGmCmGmGmAmAmAmCmGmCmC mGmGmCAAGUUAAAAUAAGGCUAGUCCGUUAU CAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmC mAmCmCmGmAmGmUmCmGmGmUmGmCmUsmUs mUsmU - NHC6-CrossL- CKRTADGSEFESPKKKRKV	1466 ; 1463
TSBTx38 35	gRNA1 202	End Mods	mUsmCsmUsCACCUCUGCAAGUAUUGGUUUUA GAGCUAGAAAUAAGCAAGUUAAAAUAAGGCUAG UCCGUUAUCAACUUGAAAAAGUGGCACCGAGU CGGUGCUsmUsmUsmU	1467
TSBTx38 35	gRNA2 447	HM01	mUsmCsmUsCACCUCUGCAAGUAUUGGUUUUA GAmGmCmUmAmGmAmAmUmAmGmCAAGUUA AAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmG mAmAmAmAmGmUmGmGmCmAmCmCmGmAmG mUmCmGmGmUmGmCmUsmUsmUsmU	1468
TSBTx38 35	gRNA2 448	HM07	mUsmCsmUsmCmAmCmCmUmCmUGCAAGUAUU GmGUUUUAGmAmGmCmUmAmGmAmAmAmUmAm GmCmAmAGUUmAAmAAmUAmAmGmGmCmUmAG UmCmCGUUAUmCAAmCmUmUmGmAmAmAmAm AmGmUmGGmCmAmCmCmGmAmGmUmCmGmGmU mGmCmUsmUsmU	1469
TSBTx38 35	gRNA2 449	NLS (bpsv40)	mUsmCsmUsCACCUCUGCAAGUAUUGGUUUUA GAGCUAGAAAUAAGCAAGUUAAAAUAAGGCUAG UCCGUUAUCAACUUGAAAAAGUGGCACCGAGU CGGUGCmUsmUsmU - NHC6-CrossL-ac- CKRTADGSEFESPKKKRKV	1470 ; 1463
TSBTx38 35	gRNA2 450	Hairpin Extension (LONGEST T-OLD)	mUsmCsmUsCACCUCUGCAAGUAUUGGUUUUA GAmGmCmCmGmGmCmGmGmAmAmAmCmGmCmC mGmGmCAAGUUAAAAUAAGGCUAGUCCGUUAU CAmAmCmUmUmGmAmAmAmAmAmGUGmGmCmA mCmCmGmAmGmUmCmGmGmUmGmCmUsmUsmU	1471

Target Site Name	Guide polynucleotide name	Nucleotide Modification Scheme	Guide polynucleotide sequence	SEQ ID NO
TSBTx3835	gRNA3337	LONGEST	mUsmCsmUsCACCUCUGCAAGUAUUGGUUUUA GAmGmCmCmGmGmCmGmGmAmAmAmCmGmCmC mGmGmCAAGUUAAAAUAAGGCUAGUCCGUUAU CAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmC mAmCmCmGmAmGmUmCmGmGmUmGmCmUsmUs mUsmU	1472
TSBTx3835	gRNA3338	LONGEST +NLS	mUsmGsmUsCACCUCUGCAAGUAUUGGUUUUA GAmGmCmCmGmGmCmGmGmAmAmAmCmGmCmC mGmGmCAAGUUAAAAUAAGGCUAGUCCGUUAU CAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmC mAmCmCmGmAmGmUmCmGmGmUmGmCmUsmUs mUsmU - NHC5-CrossL- CKRTADGSEFESP KKKRKV	1473 ; 1463
TSBTx3837	gRNA2067	End Mods	mUsmGsmCsUUACAAUGACUGAGAUCUGUUUU AGAGCUAGAAAUAAGCAAGUUAAAAUAAGGCUA GUCCGUUAUCAACUUGAAAAAGUGGCACCGAG UCGGUGCUsmUsmUsmU	1474
TSBTx3837	gRNA2451	HM01	mUsmGsmCsUUACAAUGACUGAGAUCUGUUUU AGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUU AAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUm GmAmAmAmAmAmGmUmGmGmCmAmCmGmAm GmUmCmGmGmUmGmCmUsmUsmUsmU	1475
TSBTx3837	gRNA2452	HM07	mUsmGsmCsmUmUmAmCmAmAmUmGACUGAGA UCUmGUUUUAGmAmGmCmUmAmGmAmAmAmUm AmGmCmAmAGUUmAAmAAmUAmAmGmGmCmUm AGUmCmCGUUAUmCAAmCmUmUmGmAmAmAm AmAmGmUmGGmCmAmCmCmGmAmGmUmCmGmG mUmGmCmUsmUsmUsmU	1476
TSBTx3837	gRNA2453	NLS (bpsv40)	mUsmGsmCsUUACAAUGACUGAGAUCUGUUUU AGAGCUAGAAAUAAGCAAGUUAAAAUAAGGCUA GUCCGUUAUCAACUUGAAAAAGUGGCACCGAG UCGGUGCmUsmUsmUsU - NHC6-CrossL-ac- CKRTADGSEFESP KKKRKV	1477 ; 1463
TSBTx3837	gRNA2454	Hairpin Extension (LONGEST-OLD)	mUsmGsmCsUUACAAUGACUGAGAUCUGUUUU AGAmGmCmCmGmGmCmGmGmAmAmAmCmGmCm CmGmGmCAAGUUAAAAUAAGGCUAGUCCGUUA UCAmAmCmUmUmGmAmAmAmAmAmGUGmGmCm AmCmCmGmAmGmUmCmGmGmUmGmCmUsmUsm UsmU	1478
TSBTx3837	gRNA3339	LONGEST	mUsmGsmCsUUACAAUGACUGAGAUCUGUUUU AGAmGmCmCmGmGmCmGmGmAmAmAmCmGmCm CmGmGmCAAGUUAAAAUAAGGCUAGUCCGUUA UCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGm CmAmCmCmGmAmGmUmCmGmGmUmGmCmUsmU smUsmU	1479

Target Site Name	Guide polynucleotide name	Nucleotide Modification Scheme	Guide polynucleotide sequence	SEQ ID NO
TSBTx3837	gRNA3340	LONGEST +NLS	mUsmGsmCsUUACAAUGACUGAGAUCUGUUUU AGAmGmCmCmGmGmCmGmGmAmAmAmCmGmCm CmGmGmCAAGUUAAAAUAAGGCUAGUCCGUUA UCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGm CmAmCmCmGmAmGmUmCmGmGmUmGmCmUsmU smUsmU - NHC5-CrossL- CKRTADGSEFESPKKKRKV	1480 ; 1463
TSBTx3837 (NHP)	gRNA2072	End Mods	mUsmGsmCsUUACAGUGACUGAGAUCUGUUUU AGAGCUAGAAAUAAGCAAGUUAAAAUAAGGCUA GUCCGUUAUCAACUUGAAAAAGUGGCACCGAG UCGGUGCUsmUsmUsmU	1481
TSBTx3837 (NHP)	gRNA5856	HM01	mUsmGsmCsUUACAGUGACUGAGAUCUGUUUU AGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUU AAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUm GmAmAmAmAmAmGmUmGmGmCmAmCmGmAm GmUmCmGmGmUmGmCmUsmUsmUsmU	1482

Table 1G: Alternative names for guide polynucleotides.

Guide Name	Alternative Guide Name
gRNA1193	gRNA1193-1862
gRNA2210	gRNA1193-1863
gRNA2444	gRNA2444-1992
gRNA2445	gRNA2445-1993
gRNA2446	gRNA2446-1994
gRNA3335	gRNA3335-3047
gRNA3336	gRNA3336-3048
gRNA1202	gRNA1202-1995
gRNA2447	gRNA2447-4112
gRNA2448	gRNA2448-4113
gRNA2449	gRNA2449-4114
gRNA3337	gRNA3337-3049
gRNA3338	gRNA3338-3050
gRNA2067	gRNA2067-1996
gRNA2451	gRNA2451-1997
gRNA2452	gRNA2452-1998
gRNA2453	gRNA2453-1999
gRNA2454	gRNA2454-2000
gRNA3339	gRNA3339-3051
gRNA3340	gRNA3340-3052

Table 2A. Representative spacer and target site sequences relating to disruption of a complement factor B splice site using base editing.

Guide polynucleotide name	Alterantive name	Target site name	Protospacer sequence	SEQ ID NO
gRNA2055	gRNA1193_19nt	TSBTx3826	CTCAGATGTCTATGTGTTT	1483
gRNA1193	gRNA1193_20nt	TSBTx3826	CCTCAGATGTCTATGTGTTT	1484
gRNA2057	gRNA1193_21nt	TSBTx3826	CCCTCAGATGTCTATGTGTTT	1485
gRNA2058	gRNA1193_22nt	TSBTx3826	TCCCTCAGATGTCTATGTGTTT	1486
gRNA2059	gRNA1193_23nt	TSBTx3826	ATCCCTCAGATGTCTATGTGTTT	1487
gRNA2060	gRNA1202_19nt	TSBTx3835	CTCACCTCTGCAAGTATTG	1488
gRNA1202	gRNA1202_20nt	TSBTx3835	TCTCACCTCTGCAAGTATTG	1489
gRNA2062	gRNA1202_21nt	TSBTx3835	CTTCACCTCTGCAAGTATTG	1490
gRNA2063	gRNA1202_22nt	TSBTx3835	TCTCTCACCTCTGCAAGTATTG	1491
gRNA2064	gRNA1202_23nt	TSBTx3835	TTCTCTCACCTCTGCAAGTATTG	1492
gRNA2065	gRNA1204_19nt	TSBTx3837	CTTACAATGACTGAGATCT	1493
gRNA1204	gRNA1204_20nt	TSBTx3837	GCTTACAATGACTGAGATCT	1494
gRNA2067	gRNA1204_21nt	TSBTx3837	TGCTTACAATGACTGAGATCT	1495
gRNA2068	gRNA1204_22nt	TSBTx3837	GTGCTTACAATGACTGAGATCT	1496
gRNA2069	gRNA1204_23nt	TSBTx3837	TGTGCTTACAATGACTGAGATCT	1497
gRNA2070	gRNA1999_NHP19nt	TSBTx4943	CTTACAGTGACTGAGATCT	1498
gRNA1999	gRNA1999_NHP20nt	TSBTx4943	GCTTACAGTGACTGAGATCT	1499
gRNA2072	gRNA1999_NHP21nt	TSBTx4943	TGCTTACAGTGACTGAGATCT	1500
gRNA2073	gRNA1999_NHP22nt	TSBTx4943	GTGCTTACAGTGACTGAGATCT	1501
gRNA2074	gRNA1999_NHP23nt	TSBTx4943	TGTGCTTACAGTGACTGAGATCT	1502

Table 2A (CONTINUED).

Guide polynucleotide name	Target site sequence ⁷	SEQ ID NO	Spacer sequence	SEQ ID NO
gRNA2055	CTC AG ATGTCTATGTGTTT <u>GG</u>	1503	CUCAGAUGUCUAUGUGUUU	1523
gRNA1193	CCTC AG ATGTCTATGTGTTT <u>GGG</u>	1504	CCUCAGAUGUCUAUGUGUUU	1524

⁷ PAM sequences shown as underlined plain text; target nucleotides are in bold; human sequence nucleotides complementary to a primate (cyno) target sequence but not to a human target sequence are in bold underline.

Guide polynucleotide name	Target site sequence ⁷	SEQ ID NO	Spacer sequence	SEQ ID NO
gRNA2057	CCCTC A GATGTCTATGTGTT TGGG	1505	CCCUCAGAUGUCUAUGUG UUU	1525
gRNA2058	TCCCTC A GATGTCTATGTGT TTGGG	1506	UCCCUCAGAUGUCUAUGU GUUU	1526
gRNA2059	ATCCCTC A GATGTCTATGTG TTTGGG	1507	AUCCCUCAGAUGUCUAUG UGUUU	1527
gRNA2060	CTC A CCTCTGCAAGTATTGG GG	1508	CUCACCUCUGCAAGUAU G	1528
gRNA1202	TCTC A CCTCTGCAAGTATTG GGG	1509	UCUCACCUCUGCAAGUAU UG	1529
gRNA2062	CTCTC A CCTCTGCAAGTATT GGGG	1510	CUCUCACCUCUGCAAGUA UUG	1530
gRNA2063	TCTCTC A CCTCTGCAAGTAT TGGGG	1511	UCUCUCACCUCUGCAAGU AUUG	1531
gRNA2064	TTCTCTC A CCTCTGCAAGTA TTGGGG	1512	UUCUCUCACCUCUGCAAG UAUUG	1532
gRNA2065	CTT A CAATGACTGAGATCTT GG	1513	CUUACAAUGACUGAGAUC U	1533
gRNA1204	GCTT A CAATGACTGAGATCT TGG	1514	GCUUACAAUGACUGAGAU CU	1534
gRNA2067	TGCTT A CAATGACTGAGATC TTGG	1515	UGC UUACAAUGACUGAGA UCU	1535
gRNA2068	GTGCTT A CAATGACTGAGAT CTTGG	1516	GUGCUUACAAUGACUGAG AUCU	1536
gRNA2069	TGTGCTT A CAATGACTGAGA TCTTGG	1517	UGUGCUUACAAUGACUGA GAUCU	1537
gRNA2070	CTT A CAGTGACTGAGATCTT GG	1518	CUUACAGUGACUGAGAUC U	1538
gRNA1999	GCTT A CAGTGACTGAGATCT TGG	1519	GCUUACAGUGACUGAGAU CU	1539
gRNA2072	TGCTT A CAGTGACTGAGATC TTGG	1520	UGC UUACAGUGACUGAGA UCU	1540
gRNA2073	GTGCTT A CAGTGACTGAGAT CTTGG	1521	GUGCUUACAGUGACUGAG AUCU	1541
gRNA2074	TGTGCTT A CAGTGACTGAGA TCTTGG	1522	UGUGCUUACAGUGACUGA GAUCU	1542

Table 2B. Representative spacer and target site sequences relating to disrupting of a complement factor B splice site or introducing a new stop codon into a complement factor B polynucleotide using base editing.

Guide polynucleotide name	Target site name	Target site	SEQ ID NO	Spacer sequence	SEQ ID NO	Editor
gRNA1181	TSBTx 3814	CTGCAGGATTGCAC AACATG	1743	CUGCAGGAUUGCA CAACAUG	1899	ABE_NGC_20 nt 3-9_008
gRNA1182	TSBTx 3815	ATAGGCCCATTTGT CTCCCC	1744	AUAGGCCCAUUUG UCUCCCC	1900	ABE_NGC_20 nt 3-9_008
gRNA1183	TSBTx 3816	CTCTGCAGGTTGGT GTAATC	1745	CUCUGCAGGUUGG UGUAAUC	1901	ABE_NGC_20 nt 3-9_008

gRNA1184	TSBTx 3817	ACGCTCTCACCTGA TAGTCT	1746	ACGCUCUCACCUG AUAGUCU	1902	ABE_NGC_20 nt 3-9 008
gRNA1185	TSBTx 3818	CTTACAATGACTGA GATCTT	1747	CUUACAAUGACUG AGAUCUU	1903	ABE_NGC_20 nt 3-9 008
gRNA1186	TSBTx 3819	TCACCTCCGTTGTC ACAGAT	1748	UCACCUCCGUUGU CACAGAU	1904	ABE_NGC_20 nt 3-9 008
gRNA1187	TSBTx 3820	TCGCTTACCTCCAG ACAAGA	1749	UCGCUUACCUCCA GACAAGA	1905	ABE_NGC_20 nt 3-9 008
gRNA1188	TSBTx 3821	CACCCACAGGTGGC AAGTTA	1750	CACCCACAGGUGG CAAGUUA	1906	ABE_NGG_20 nt 3-9 002
gRNA1189	TSBTx 3822	ACAGACCACAAGTT GAAGTC	1751	ACAGACCACAAGU UGAAGUC	1907	ABE_NGG_20 nt 3-9 002
gRNA1190	TSBTx 3823	TCTGCAGGATTGCA CAACAT	1752	UCUGCAGGAUUGC ACAACAU	1908	ABE_NGG_20 nt 3-9 002
gRNA1191	TSBTx 3824	GCAGATTGCACAA CATGGG	1753	GCAGGAUUGCACA ACAUGGG	1909	ABE_NGG_20 nt 3-9 002
gRNA1192	TSBTx 3825	CCCTCAGATGTCTA TGTGTT	1754	CCCUCAGAUGUCU AUGUGUU	1910	ABE_NGG_20 nt 3-9 002
gRNA1193	TSBTx 3826	CCTCAGATGTCTAT GTGTTT	1755	CCUCAGAUGUCUA UGUGUUU	1911	ABE_NGG_20 nt 3-9 002
gRNA1194	TSBTx 3827	CTCAGATGTCTATG TGTTTG	1756	CUCAGAUGUCUAU GUGUUUG	1912	ABE_NGG_20 nt 3-9 002
gRNA1195	TSBTx 3828	GTGTCCCAGCGCC CTTCAA	1757	GUGUCCCAGCGC CCUUCAA	1913	ABE_NGG_20 nt 3-9 002
gRNA1196	TSBTx 3829	TGTCCCAGCGCCC TTCAAA	1758	UGUCCCAGCGCC CUUCAAA	1914	ABE_NGG_20 nt 3-9 002
gRNA1197	TSBTx 3830	CTACTTCAGGAGGG GAGAAG	1759	CUACUUCAGGAGG GGAGAAG	1915	ABE_NGG_20 nt 3-9 002
gRNA1198	TSBTx 3831	TACTTCAGGAGGGG AGAAGC	1760	UACUUCAGGAGGG GAGAAGC	1916	ABE_NGG_20 nt 3-9 002
gRNA1199	TSBTx 3832	CTCCTTGCAGGTGA TTCTGG	1761	CUCCUUCAGGUG AUUCUGG	1917	ABE_NGG_20 nt 3-9 002
gRNA1200	TSBTx 3833	TGCAGGTTGGTGTA ATCAGC	1762	UGCAGGUUGGUGU AAUCAGC	1918	ABE_NGG_20 nt 3-9 002
gRNA1201	TSBTx 3834	GCAGGTTGGTGTA TCAGCT	1763	GCAGGUUGGUGUA AUCAGCU	1919	ABE_NGG_20 nt 3-9 002
gRNA1202	TSBTx 3835	TCTCACCTCTGCAA GTATTG	1764	UCUCACCUCUGCA AGUAUUG	1920	ABE_NGG_20 nt 3-9 002
gRNA1203	TSBTx 3836	CTTACTTTGTTGCT GGCAAG	1765	CUUACUUUGUUGC UGGCAAG	1921	ABE_NGG_20 nt 3-9 002
gRNA1204	TSBTx 3837	GCTTACAATGACTG AGATCT	1766	GCUUACAAUGACU GAGAUCU	1922	ABE_NGG_20 nt 3-9 002
gRNA1205	TSBTx 3838	TCACCCAGATAATC CTCCCT	1767	UCACCCAGAUAAU CCUCCCU	1923	ABE_NGG_20 nt 3-9 002
gRNA1206	TSBTx 3839	CCTTCTGACCATCA GTCATG	1768	CCUUCUGACCAUC AGUCAUG	1924	ABE_NGG_20 nt 3-9 002
gRNA1207	TSBTx 3840	CAAAGGTCACCTTG GCAGGA	1769	CAAAGGUCACCUU GGCAGGA	1925	ABE_NGG_20 nt 3-9 002
gRNA1208	TSBTx 3841	CTCGCTTACCTCCA GACAAG	1770	CUCGCUUACCUC AGACAAG	1926	ABE_NGG_20 nt 3-9 002
gRNA1209	TSBTx 3842	TCAAAGCAATCCAC TGTTCA	1771	UCAAGCAAUCCA CUGUCCA	1927	ABE_NGA_20 nt 3-9 005
gRNA1210	TSBTx 3843	CTCCAGACTCCTT CATGTA	1772	CUCCAGACUCCU UCAUGUA	1928	ABE_NGA_20 nt 3-9 005

gRNA1211	TSBTx 3844	CCCAGGGGAACAAC AGAAGC	1773	CCCAGGGGAACAA CAGAAGC	1929	ABE_NGA_20 nt 3-9 005
gRNA1212	TSBTx 3845	ACAGGTGGCAAGTT ATGGTG	1774	ACAGGUGGCAAGU UAUGGUG	1930	ABE_NGA_20 nt 3-9 005
gRNA1213	TSBTx 3846	GCCAGATGAAAGCC AGTCTC	1775	GCCAGAUGAAAGC CAGUCUC	1931	ABE_NGA_20 nt 3-9 005
gRNA1214	TSBTx 3847	GTCCCCAGCGCCCT TCAAAG	1776	GUCCCCAGCGCCC UUCAAAG	1932	ABE_NGA_20 nt 3-9 005
gRNA1215	TSBTx 3848	TACAGAAAGGCAGC TGTGAG	1777	UACAGAAAGGCAG CUGUGAG	1933	ABE_NGA_20 nt 3-9 005
gRNA1216	TSBTx 3849	GAGGACTCACTTGA ATGAAA	1778	GAGGACUCACUUG AAUGAAA	1934	ABE_NGA_20 nt 3-9 005
gRNA1217	TSBTx 3850	TCTCACCTTATCCC CATTCT	1779	UCUCACCUUAUCC CCAUUCU	1935	ABE_NGA_20 nt 3-9 005
gRNA1218	TSBTx 3851	ATCCTTACCTACGC TGACCT	1780	AUCCUUACCUACG CUGACCU	1936	ABE_NGA_20 nt 3-9 005
gRNA1219	TSBTx 3852	TTACCTACGCTGAC CTTGAT	1781	UUACCUACGCUGA CCUUGAU	1937	ABE_NGA_20 nt 3-9 005
gRNA1220	TSBTx 3853	CTCCCTACCGATCA TTTGGT	1782	CUCCCUACCGAUC AUUUGGU	1938	ABE_NGA_20 nt 3-9 005
gRNA1221	TSBTx 3854	CTGACCATCAGTCA TGAGGA	1783	CUGACCAUCAGUC AUGAGGA	1939	ABE_NGA_20 nt 3-9 005
gRNA1222	TSBTx 3855	CTTCTCACCTCCGT TGTCAC	1784	CUUCUCACCUCCG UUGUCAC	1940	ABE_NGA_20 nt 3-9 005
gRNA1223	TSBTx 3856	TCCCTCAGATGTCT ATGTGTT	1785	UCCUCAGAUGUC UAUGUGUU	1941	ABE_NNGRR T_2Int_5- 14 011
gRNA1224	TSBTx 3857	CTGCCAGATGAAAG CCAGTCT	1786	CUGCCAGAUGAAA GCCAGUCU	1942	ABE_NNGRR T_2Int_5- 14 011
gRNA1225	TSBTx 3858	TTCTCTCACCTCTG CAAGTAT	1787	UUCUCUACCUCU GCAAGUUAU	1943	ABE_NNGRR T_2Int_5- 14 011
gRNA1226	TSBTx 3859	CCTTACCTACGCTG ACCTTGA	1788	CCUUACCUACGCU GACCUUGA	1944	ABE_NNGRR T_2Int_5- 14 011
gRNA1227	TSBTx 3860	ACTCACCCAGATAA TCCTCCC	1789	ACUCACCCAGAU AUCCUCCC	1945	ABE_NNGRR T_2Int_5- 14 011
gRNA1228	TSBTx 3861	TCCCTTCTGACCAT CAGTCAT	1790	UCCCUUCUGACCA UCAGUCAU	1946	ABE_NNGRR T_2Int_5- 14 011
gRNA1229	TSBTx 3862	CTTCAGGTGTGACC ACCACTC	1791	CUUCAGGUGUGAC CACCACUC	1947	ABE_NNNRR T_2Int_5- 14 014
gRNA1230	TSBTx 3863	CCCTCTCCACAGAC CACAAGT	1792	CCCUCUCCACAGA CCACAAGU	1948	ABE_NNNRR T_2Int_5- 14 014
gRNA1231	TSBTx 3864	CTACAGAAAGGCAG CTGTGAG	1793	CUACAGAAAGGCA GCUGUGAG	1949	ABE_NNNRR T_2Int_5- 14 014
gRNA1232	TSBTx 3865	GTATGTCTTACTTT GTTGCTG	1794	GUAUGUCUUACUU UGUUGCUG	1950	ABE_NNNRR T_2Int_5- 14 014

gRNA1233	TSBTx 3866	TGTCTTACTTTGTT GCTGGCA	1795	UGUCUUACUUUGU UGCUGGCA	1951	ABE_NNNRR T_2Int_5- 14_014
gRNA1234	TSBTx 3867	TGCATCCTTACCTA CGCTGAC	1796	UGCAUCCUUACCU ACGCUGAC	1952	ABE_NNNRR T_2Int_5- 14_014
gRNA1235	TSBTx 3868	GGATTCTGTGCTTA CAATGAC	1797	GGAUUCUGUGCUU ACAAUGAC	1953	ABE_NNNRR T_2Int_5- 14_014
gRNA1236	TSBTx 3869	CTTGATCTCTCCCTA CCGATCA	1798	CUUGUAUCUCCCU ACCGAUCA	1954	ABE_NNNRR T_2Int_5- 14_014
gRNA1237	TSBTx 3870	CTTCTGACCATCAG TCATGAG	1799	CUUCUGACCAUCA GUCAUGAG	1955	ABE_NNNRR T_2Int_5- 14_014
gRNA1238	TSBTx 3871	CCCTAACCTCTGAC CTTCATA	1800	CCCUAACCUCUGA CCUUCAUA	1956	ABE_NNNRR T_2Int_5- 14_014
gRNA1239	TSBTx 3872	AGGAGGATTCCACC TTCTCAA	1801	AGGAGGAUUCAC CUUCUCAA	1957	ABE_NNNRR T_2Int_5- 14_014
gRNA1240	TSBTx 3873	ATGCTTCTCACCTC CGTTGTC	1802	AUGCUUCUACCU CCGUUGUC	1958	ABE_NNNRR T_2Int_5- 14_014
gRNA1241	TSBTx 3874	TTCTCCAAGAGGGC CAGGCAC	1803	UUCUCCAAGAGGG CCAGGCAC	1959	CBE_NNGRRT _2Int_3- 12_012
gRNA1242	TSBTx 3875	ACCAAAAGACTGTC AGGAAGG	1804	ACCAAAAGACUGU CAGGAAGG	1960	CBE_NNGRRT _2Int_3- 12_012
gRNA1243	TSBTx 3876	ACCTGCCAAGTGAA TGGCCGA	1805	ACCUGCCAAGUGA AUGGCCGA	1961	CBE_NNGRRT _2Int_3- 12_012
gRNA1244	TSBTx 3877	GAGCAACATGTGTT CAAAGTC	1806	GAGCAACAUGUGU UCAAGUC	1962	CBE_NNGRRT _2Int_3- 12_012
gRNA1245	TSBTx 3878	TACACCAACCTGCA GAGGCAG	1807	UACACCAACCUGC AGAGGCAG	1963	CBE_NNGRRT _2Int_3- 12_012
gRNA1246	TSBTx 3879	GGCTTTCATCTGGC AGAGAAG	1808	GGCUUUCUUCUGG CAGAGAAG	1964	CBE_NNGRRT _2Int_3- 12_012
gRNA1247	TSBTx 3880	GACATCTGAGGGAT AAAAAGG	1809	GACAUCUGAGGGA UAAAAAGG	1965	CBE_NNGRRT _2Int_3- 12_012
gRNA1248	TSBTx 3881	TGTTGTTCCCTGG GTGCCAG	1810	UGUUGUUCUCCUG GGUGCCAG	1966	CBE_NNGRRT _2Int_3- 12_012
gRNA1249	TSBTx 3882	ATCGCACCTGCCAA GTGAATG	1811	AUCGCACCUGCCA AGUGAAUG	1967	CBE_NNNRRT _2Int_3- 12_015
gRNA1250	TSBTx 3883	TGGCCGATGGAGTG GGCAGAC	1812	UGGCCGAUGGAGU GGGCAGAC	1968	CBE_NNNRRT _2Int_3- 12_015

gRNA1251	TSBTx 3884	TCCCAGCGGCGAAC GTGTCAG	1813	UCCCAGCGGCGAA CGUGUCAG	1969	CBE_NNNRRT _2Int_3- 12_015
gRNA1252	TSBTx 3885	CCCAGGGGAACAAC AGAAGCG	1814	CCCAGGGGAACAA CAGAAGCG	1970	CBE_NNNRRT _2Int_3- 12_015
gRNA1253	TSBTx 3886	GTCACGAAGCAGCT CAATGAA	1815	GUCACGAAGCAGC UCAAUGAA	1971	CBE_NNNRRT _2Int_3- 12_015
gRNA1254	TSBTx 3887	GGCCCTCCAGGCAG TGTACAG	1816	GGCCCUCCAGGCA GUGUACAG	1972	CBE_NNNRRT _2Int_3- 12_015
gRNA1255	TSBTx 3888	TTTCTACCAAATGA TCGGTAG	1817	UUUCUACCAAAUG AUCGGUAG	1973	CBE_NNNRRT _2Int_3- 12_015
gRNA1256	TSBTx 3889	GCAACCATGGCAGG CCAAGAT	1818	GCAACCAUGGCAG GCCAAGAU	1974	CBE_NNNRRT _2Int_3- 12_015
gRNA1257	TSBTx 3890	TCAGCCAGGGCAGC ACTTGAA	1819	UCAGCCAGGGCAG CACUUGAA	1975	CBE_NNNRRT _2Int_3- 12_015
gRNA1258	TSBTx 3891	CTTACTTTGTTGCT GGCAAGT	1820	CUUACUUUGUUGC UGGCAAGU	1976	CBE_NNNRRT _2Int_3- 12_015
gRNA1259	TSBTx 3892	CTCCCTCCTGAAG TAGGAGA	1821	CUCCCCUCCUGAA GUAGGAGA	1977	CBE_NNNRRT _2Int_3- 12_015
gRNA1260	TSBTx 3893	TTTGAAGGGCGCTG GGGACAC	1822	UUUGAAGGGCGCU GGGGACAC	1978	CBE_NNNRRT _2Int_3- 12_015
gRNA1261	TSBTx 3894	TCTTGGCCTGCCAT GGTTGCT	1823	UCUUGGCCUGCCA UGGUUGCU	1979	CBE_NNNRRT _2Int_3- 12_015
gRNA1262	TSBTx 3895	TGGCCTGCCATGGT TGCTTGT	1824	UGGCCUGCCAUGG UUGCUUGU	1980	CBE_NNNRRT _2Int_3- 12_015
gRNA1263	TSBTx 3896	ATGAAGGAGTCTGG GAGAGTC	1825	AUGAAGGAGUCUG GGAGAGUC	1981	CBE_NNNRRT _2Int_3- 12_015
gRNA1264	TSBTx 3897	GGAGTCTGGGAGAG TCAGAAA	1826	GGAGUCUGGGAGA GUCAGAAA	1982	CBE_NNNRRT _2Int_3- 12_015
gRNA1265	TSBTx 3898	CGCTGCAGAGGTAT GAGACAT	1827	CGCUGCAGAGGUA UGAGACAU	1983	CBE_NNNRRT _2Int_3- 12_015
gRNA1266	TSBTx 3899	ACTCCATCGGCCAT TCACTTG	1828	ACUCCAUCGGCCA UUCACUUG	1984	CBE_NNNRRT _2Int_3- 12_015
gRNA1267	TSBTx 3900	GGGGCCAGTATTCC CCGTTCT	1829	GGGGCCAGUAUUC CCCJUUCU	1985	CBE_NNNRRT _2Int_3- 12_015
gRNA1268	TSBTx 3901	GGATTGCTTTGAGA AGGGGGG	1830	GGAUUGCJUUGAG AAGGGGGG	1986	CBE_NNNRRT _2Int_3- 12_015

gRNA1269	TSBTx 3902	TTCAGGGTGCTCCA GGACCCC	1831	UUCAGGGUGCUCC AGGACCCC	1987	CBE_NNNRRT _21nt_3- 12_015
gRNA1270	TSBTx 3903	GCTCCAGGACCCCG TAGATCT	1832	GCUCCAGGACCCC GUAGAUCU	1988	CBE_NNNRRT _21nt_3- 12_015
gRNA1271	TSBTx 3943	TGGTCACACCTGAA GAGAAAAG	1833	UGGUCACACCUGA AGAGAAAAG	1989	CBE_NNNRRT _21nt_3- 12_015
gRNA1272	TSBTx 3944	CTTACCTCCAGACA AGAGGCC	1834	CUUACCUCCAGAC AAGAGGCC	1990	CBE_NNNRRT _21nt_3- 12_015
gRNA1356	TSBTx 3997	CTCCTTCCGACTTC TCCAAG	1835	CUCCUCCGACUUC CUCCAAG	1991	CBE_NGG_20 nt_4-9_003
gRNA1357	TSBTx 3998	TCCTTCCGACTTCT CCAAGA	1836	UCCUCCGACUUC UCCAAGA	1992	CBE_NGG_20 nt_4-9_003
gRNA1358	TSBTx 3999	TCTCCAAGAGGGCC AGGCAC	1837	UCUCCAAGAGGGC CAGGCAC	1993	CBE_NGG_20 nt_4-9_003
gRNA1359	TSBTx 4000	CTCAAGACCAAAAAG ACTGTC	1838	CUCAAGACCAAAA GACUGUC	1994	CBE_NGG_20 nt_4-9_003
gRNA1360	TSBTx 4001	AGACCAAAAGACTG TCAGGA	1839	AGACCAAAAGACU GUCAGGA	1995	CBE_NGG_20 nt_4-9_003
gRNA1361	TSBTx 4002	CCTGCCAAGTGAAT GGCCGA	1840	CCUGCCAAGUGAA UGGCCGA	1996	CBE_NGG_20 nt_4-9_003
gRNA1362	TSBTx 4003	CTCCCAGCGGCGAA CGTGTC	1841	CUCCCAGCGGCGA ACGUGUC	1997	CBE_NGG_20 nt_4-9_003
gRNA1363	TSBTx 4004	CAGCGGCGAACGTG TCAGGA	1842	CAGCGGCGAACGU GUCAGGA	1998	CBE_NGG_20 nt_4-9_003
gRNA1364	TSBTx 4005	CGGCGAACGTGTCA GGAAGG	1843	CGGCGAACGUGUC AGGAAGG	1999	CBE_NGG_20 nt_4-9_003
gRNA1365	TSBTx 4006	CGTGTCAGGAAGGT GGCTCT	1844	CGUGUCAGGAAGG UGGCUCU	2000	CBE_NGG_20 nt_4-9_003
gRNA1366	TSBTx 4007	TTTCTACCAAATG ATCGGT	1845	UUUUCUACCAAU GAUCGGU	2001	CBE_NGG_20 nt_4-9_003
gRNA1367	TSBTx 4008	TTTCTACCAAATGA TCGGTA	1846	UUUCUACCAAUG AUCGGUA	2002	CBE_NGG_20 nt_4-9_003
gRNA1368	TSBTx 4009	GCAACAAAGTAAGA CATACT	1847	GCAACAAAGUAAG ACAUACU	2003	CBE_NGG_20 nt_4-9_003
gRNA1369	TSBTx 4010	ACCTCTTTCAAGTG CTGCCC	1848	ACCUCUUUCAAGU GCUGCCC	2004	CBE_NGG_20 nt_4-9_003
gRNA1370	TSBTx 4011	GAAACTCCAAGATG AGGATT	1849	GAAACUCCAAGAU GAGGAUU	2005	CBE_NGG_20 nt_4-9_003
gRNA1371	TSBTx 4012	AAACTCCAAGATGA GGATTT	1850	AAACUCCAAGAUG AGGAUUU	2006	CBE_NGG_20 nt_4-9_003
gRNA1372	TSBTx 4013	CACCAACCTGCAGA GGCAGT	1851	CACCAACCUGCAG AGGCAGU	2007	CBE_NGG_20 nt_4-9_003
gRNA1373	TSBTx 4014	ACCAACCTGCAGAG GCAGTG	1852	ACCAACCUGCAGA GGCAGUG	2008	CBE_NGG_20 nt_4-9_003
gRNA1374	TSBTx 4015	TGCCTTTCTGTAGG GGAGGT	1853	UGCCUUUCUGUAG GGGAGGU	2009	CBE_NGG_20 nt_4-9_003
gRNA1375	TSBTx 4016	AAATGGGCCTATAA AGGACA	1854	AAAUGGGCCUAUA AAGGACA	2010	CBE_NGG_20 nt_4-9_003
gRNA1376	TSBTx 4017	CCCTCCTGAAGTAG GAGAGT	1855	CCCUCCUGAAGUA GGAGAGU	2011	CBE_NGG_20 nt_4-9_003

gRNA1377	TSBTx 4018	TGGCCTGCCATGGT TGCTTG	1856	UGGCCUGCCAUGG UUGCUUG	2012	CBE_NGG_20 nt 4-9 003
gRNA1378	TSBTx 4019	TAGACATCTGAGGG ATAAAA	1857	UAGACAUCUGAGG GAUAAAA	2013	CBE_NGG_20 nt 4-9 003
gRNA1379	TSBTx 4020	CATCTGAGGGATAA AAAGGA	1858	CAUCUGAGGGGAUA AAAAGGA	2014	CBE_NGG_20 nt 4-9 003
gRNA1380	TSBTx 4021	TGCAATCCTGCAGA AGAGAC	1859	UGCAAUCCUGCAG AAGAGAC	2015	CBE_NGG_20 nt 4-9 003
gRNA1381	TSBTx 4022	GTGCGGTTCCAGCC TTCAGG	1860	GUGCGGUUCCAGC CUUCAGG	2016	CBE_NGG_20 nt 4-9 003
gRNA1382	TSBTx 4023	TGCGGTTCCAGCCT TCAGGA	1861	UGCGGUUCCAGCC UUCAGGA	2017	CBE_NGG_20 nt 4-9 003
gRNA1383	TSBTx 4024	GACCCAAATTTTGG GGTATG	1862	GACCCAAAUUUUG GGGUAUG	2018	CBE_NGG_20 nt 4-9 003
gRNA1384	TSBTx 4025	CACTCCATCGGCCA TTCAC	1863	CACUCCAUCGGCC AUUCACU	2019	CBE_NGG_20 nt 4-9 003
gRNA1385	TSBTx 4026	GTGGATTGCTTTGA GAAGGG	1864	GUGGAUUGCUUUG AGAAGGG	2020	CBE_NGG_20 nt 4-9 003
gRNA1386	TSBTx 4027	CCCCAGGGATCCTG CTCTCT	1865	CCCCAGGGAUCCU GCUCUCU	2021	CBE_NGA_20 nt 4-9 006
gRNA1387	TSBTx 4028	TCAAGACCAAAAGA CTGTCA	1866	UCAAGACCAAAAG ACUGUCA	2022	CBE_NGA_20 nt 4-9 006
gRNA1388	TSBTx 4029	GCACCTGCCAAGTG AATGGC	1867	GCACCUGCCAAGU GAAUGGC	2023	CBE_NGA_20 nt 4-9 006
gRNA1389	TSBTx 4030	CTGCCAAGTGAATG GCCGAT	1868	CUGCCAAGUGAAU GGCCGAU	2024	CBE_NGA_20 nt 4-9 006
gRNA1390	TSBTx 4031	GAATGGCCGATGGA GTGGGC	1869	GAAUGGCCGAUGG AGUGGGC	2025	CBE_NGA_20 nt 4-9 006
gRNA1391	TSBTx 4032	AGTGGGCAGACAGC GATCTG	1870	AGUGGGCAGACAG CGAUCUG	2026	CBE_NGA_20 nt 4-9 006
gRNA1392	TSBTx 4033	GGCAGCCAGTACCG CCTTGA	1871	GGCAGCCAGUACC GCCUUGA	2027	CBE_NGA_20 nt 4-9 006
gRNA1393	TSBTx 4034	TCCAGCGGCGAAC GTGTCA	1872	UCCAGCGGCGAA CGUGUCA	2028	CBE_NGA_20 nt 4-9 006
gRNA1394	TSBTx 4035	GTGTCAAGGAAGGTG GCTCTT	1873	GUGUCAGGAAGGU GGCUCUU	2029	CBE_NGA_20 nt 4-9 006
gRNA1395	TSBTx 4036	AGGGGAACAACAGA AGCGGA	1874	AGGGGAACAACAG AAGCGGA	2030	CBE_NGA_20 nt 4-9 006
gRNA1396	TSBTx 4037	CCTCCAGGCAGTGT ACAGCA	1875	CCUCCAGGCAGUG UACAGCA	2031	CBE_NGA_20 nt 4-9 006
gRNA1397	TSBTx 4038	TTCTACCAAATGAT CGGTAG	1876	UUCUACCAAUAUGA UCGGUAG	2032	CBE_NGA_20 nt 4-9 006
gRNA1398	TSBTx 4039	CTACCAAATGATCG GTAGGG	1877	CUACCAAUAUGAUC GGUAGGG	2033	CBE_NGA_20 nt 4-9 006
gRNA1399	TSBTx 4040	CAAGCAACCATGGC AGGCCA	1878	CAAGCAACCAUGG CAGGCCA	2034	CBE_NGA_20 nt 4-9 006
gRNA1400	TSBTx 4041	TATGGCCAGACTAT CAGGTG	1879	UAUGGCCAGACUA UCAGGUG	2035	CBE_NGA_20 nt 4-9 006
gRNA1401	TSBTx 4042	CACTTGCCAGCAAC AAAGTA	1880	CACUUGCCAGCAA CAAAGUA	2036	CBE_NGA_20 nt 4-9 006
gRNA1402	TSBTx 4043	GCTCAATATGCCCC AGGCTA	1881	GCUCAUAUGCCC CAGGCUA	2037	CBE_NGA_20 nt 4-9 006
gRNA1403	TSBTx 4044	CTTTCAAGTGCTGC CCTGGC	1882	CUUUCAAGUGCUG CCCUGGC	2038	CBE_NGA_20 nt 4-9 006

gRNA1404	TSBTx 4045	CCTTCAGCCAGGGC AGCACT	1883	CCUUCAGCCAGGG CAGCACU	2039	CBE_NGA_20 nt 4-9_006
gRNA1405	TSBTx 4046	CAGCCAGGGCAGCA CTTGAA	1884	CAGCCAGGGCAGC ACUUGAA	2040	CBE_NGA_20 nt 4-9_006
gRNA1406	TSBTx 4047	GCCTTTCTGTAGGG GAGGTG	1885	GCCUUUCUGUAGG GGAGGUG	2041	CBE_NGA_20 nt 4-9_006
gRNA1407	TSBTx 4048	AATGGGCCTATAAA GGACAA	1886	AAUGGGCCUAUAA AGGACAA	2042	CBE_NGA_20 nt 4-9_006
gRNA1408	TSBTx 4049	TGGGCCTATAAAGG ACAAGG	1887	UGGGCCUAUAAAG GACAAGG	2043	CBE_NGA_20 nt 4-9_006
gRNA1409	TSBTx 4050	GTGTTCCCAAACCA TGCCAC	1888	GUGUCCCCAAACC AUGCCAC	2044	CBE_NGA_20 nt 4-9_006
gRNA1410	TSBTx 4051	GTTCCCAAACCATG CCACAG	1889	GUUCCCCAAACCAU GCCACAG	2045	CBE_NGA_20 nt 4-9_006
gRNA1411	TSBTx 4052	GCGGTTCCAGCCTT CAGGAG	1890	GCGGUUCCAGCCU UCAGGAG	2046	CBE_NGA_20 nt 4-9_006
gRNA1412	TSBTx 4053	TTGTGGTCTGTGGA GAGGGA	1891	UUGUGGUCUGUGG AGAGGGA	2047	CBE_NGA_20 nt 4-9_006
gRNA1413	TSBTx 4054	GAGTCTGGGAGAGT CAGAAA	1892	GAGUCUGGGAGAG UCAGAAA	2048	CBE_NGA_20 nt 4-9_006
gRNA1414	TSBTx 4055	CGCTCCAAGAGCCA CCTTCC	1893	CGCUCCAAGAGCC ACCUUCC	2049	CBE_NGA_20 nt 4-9_006
gRNA1415	TSBTx 4056	TACCCCGCTGCAGA GGTATG	1894	UACCCCGCUGCAG AGGUAUG	2050	CBE_NGA_20 nt 4-9_006
gRNA1416	TSBTx 4057	GGGCCAGTATTCCC CGTTCT	1895	GGGCCAGUAUUC CCGUUCU	2051	CBE_NGA_20 nt 4-9_006
gRNA1417	TSBTx 4058	TGGATTGCTTTGAG AAGGGG	1896	UGGAUUGC UUUGA GAAGGGG	2052	CBE_NGA_20 nt 4-9_006
gRNA1418	TSBTx 4059	AGGGTGCTCCAGGA CCCCGT	1897	AGGGUGCUCCAGG ACCCCGU	2053	CBE_NGA_20 nt 4-9_006
gRNA1419	TSBTx 4060	CACCTGAAGAGAAA GGCTGA	1898	CACCUGAAGAGAA AGGCUGA	2054	CBE_NGA_20 nt 4-9_006

Table 2C. Representative spacer and target site sequences relating to disrupting of a complement factor B splice site or introducing a new stop codon into a complement factor B polynucleotide using base editing.

Guide polynucleotide name	Editor	Cas9 variant	Target alteration description
GuideDesign10_CBE_NGA_20nt_4-9_006_-_31947177_spCas9	CBE_NGA_20nt_4-9_006	spCas9 VRQR CBE	Splice Site
GuideDesign10_CBE_NGA_20nt_4-9_006_-_31948943_spCas9	CBE_NGA_20nt_4-9_006	spCas9 VRQR CBE	Splice Site
GuideDesign10_CBE_NGA_20nt_4-9_006_-_31949542_spCas9	CBE_NGA_20nt_4-9_006	spCas9 VRQR CBE	Splice Site
GuideDesign10_CBE_NGA_20nt_4-9_006_-_31950384_spCas9	CBE_NGA_20nt_4-9_006	spCas9 VRQR CBE	Splice Site

Guide polynucleotide name	Editor	Cas9 variant	Target alteration description
GuideDesign10_CBE_NGA_20nt_4-9_006_- _31950388_spCas9	CBE_NGA_20nt_4-9_006	spCas9 VRQR CBE	Splice Site
GuideDesign10_CBE_NGA_20nt_4-9_006_- _31951227_spCas9	CBE_NGA_20nt_4-9_006	spCas9 VRQR CBE	Splice Site
GuideDesign10_CBE_NGC_20nt_4-9_009_- _31946270_spCas9	CBE_NGC_20nt_4-9_009	spCas9 NGC CBE	Splice Site
GuideDesign10_CBE_NGC_20nt_4-9_009_- _31947173_spCas9	CBE_NGC_20nt_4-9_009	spCas9 NGC CBE	Splice Site
GuideDesign10_CBE_NGC_20nt_4-9_009_- _31950129_spCas9	CBE_NGC_20nt_4-9_009	spCas9 NGC CBE	Splice Site
GuideDesign10_CBE_NGC_20nt_4-9_009_- _31951854_spCas9	CBE_NGC_20nt_4-9_009	spCas9 NGC CBE	Splice Site
GuideDesign10_CBE_NGG_20nt_4-9_003_- _31946271_spCas9	CBE_NGG_20nt_4-9_003	spCas9 CBE	Splice Site
GuideDesign10_CBE_NGG_20nt_4-9_003_- _31948947_spCas9	CBE_NGG_20nt_4-9_003	spCas9 CBE	Splice Site
GuideDesign10_CBE_NGG_20nt_4-9_003_- _31949325_spCas9	CBE_NGG_20nt_4-9_003	spCas9 CBE	Splice Site
GuideDesign10_CBE_NGG_20nt_4-9_003_- _31950130_spCas9	CBE_NGG_20nt_4-9_003	spCas9 CBE	Splice Site
GuideDesign10_CBE_NGG_20nt_4-9_003_- _31950926_spCas9	CBE_NGG_20nt_4-9_003	spCas9 CBE	Splice Site
GuideDesign10_CBE_NGG_20nt_4-9_003_- _31951456_spCas9	CBE_NGG_20nt_4-9_003	spCas9 CBE	Splice Site
GuideDesign3_ABE_NGA_20nt_3-12_019_- _31946273_spCas9	ABE_NGA_20nt_3-12_019	['spCas9 VRQR IBE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-12_019_- _31947177_spCas9	ABE_NGA_20nt_3-12_019	['spCas9 VRQR IBE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-12_019_- _31947511_spCas9	ABE_NGA_20nt_3-12_019	['spCas9 VRQR IBE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-12_019_- _31948064_spCas9	ABE_NGA_20nt_3-12_019	['spCas9 VRQR IBE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-12_019_- _31948500_spCas9	ABE_NGA_20nt_3-12_019	['spCas9 VRQR IBE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-12_019_- _31948943_spCas9	ABE_NGA_20nt_3-12_019	['spCas9 VRQR IBE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-12_019_- _31948946_spCas9	ABE_NGA_20nt_3-12_019	['spCas9 VRQR IBE']	Splice Site

Guide polynucleotide name	Editor	Cas9 variant	Target alteration description
GuideDesign3_ABE_NGA_20nt_3-12_019_-_31948949_spCas9	ABE_NGA_20nt_3-12_019	['spCas9 VRQR IBE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-12_019_-_31949542_spCas9	ABE_NGA_20nt_3-12_019	['spCas9 VRQR IBE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-12_019_-_31950136_spCas9	ABE_NGA_20nt_3-12_019	['spCas9 VRQR IBE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-12_019_-_31950384_spCas9	ABE_NGA_20nt_3-12_019	['spCas9 VRQR IBE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-12_019_-_31950388_spCas9	ABE_NGA_20nt_3-12_019	['spCas9 VRQR IBE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-12_019_-_31951227_spCas9	ABE_NGA_20nt_3-12_019	['spCas9 VRQR IBE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-12_019_-_31951591_spCas9	ABE_NGA_20nt_3-12_019	['spCas9 VRQR IBE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-12_019_+_31947000_spCas9	ABE_NGA_20nt_3-12_019	['spCas9 VRQR IBE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-12_019_+_31947734_spCas9	ABE_NGA_20nt_3-12_019	['spCas9 VRQR IBE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-12_019_+_31947933_spCas9	ABE_NGA_20nt_3-12_019	['spCas9 VRQR IBE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-12_019_+_31947939_spCas9	ABE_NGA_20nt_3-12_019	['spCas9 VRQR IBE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-12_019_+_31948369_spCas9	ABE_NGA_20nt_3-12_019	['spCas9 VRQR IBE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-12_019_+_31948818_spCas9	ABE_NGA_20nt_3-12_019	['spCas9 VRQR IBE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-12_019_+_31950044_spCas9	ABE_NGA_20nt_3-12_019	['spCas9 VRQR IBE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-12_019_+_31950277_spCas9	ABE_NGA_20nt_3-12_019	['spCas9 VRQR IBE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-12_019_+_31950611_spCas9	ABE_NGA_20nt_3-12_019	['spCas9 VRQR IBE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-12_019_+_31951331_spCas9	ABE_NGA_20nt_3-12_019	['spCas9 VRQR IBE']	Splice Site

Guide polynucleotide name	Editor	Cas9 variant	Target alteration description
GuideDesign3_ABE_NGA_20nt_3-12_019+_31951333_spCas9	ABE_NGA_20nt_3-12_019	['spCas9 VRQR IBE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-12_019+_31951335_spCas9	ABE_NGA_20nt_3-12_019	['spCas9 VRQR IBE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-9_005_-31948064_spCas9	ABE_NGA_20nt_3-9_005	['spCas9 VRQR ABE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-9_005_-31948946_spCas9	ABE_NGA_20nt_3-9_005	['spCas9 VRQR ABE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-9_005+_31950611_spCas9	ABE_NGA_20nt_3-9_005	['spCas9 VRQR ABE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-9_005+_31951331_spCas9	ABE_NGA_20nt_3-9_005	['spCas9 VRQR ABE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-9_005+_31951333_spCas9	ABE_NGA_20nt_3-9_005	['spCas9 VRQR ABE']	Splice Site
GuideDesign3_ABE_NGC_20nt_3-12_020_-31946270_spCas9	ABE_NGC_20nt_3-12_020	['spCas9 NGC IBE']	Splice Site
GuideDesign3_ABE_NGC_20nt_3-12_020_-31946593_spCas9	ABE_NGC_20nt_3-12_020	['spCas9 NGC IBE']	Splice Site
GuideDesign3_ABE_NGC_20nt_3-12_020_-31947173_spCas9	ABE_NGC_20nt_3-12_020	['spCas9 NGC IBE']	Splice Site
GuideDesign3_ABE_NGC_20nt_3-12_020_-31947507_spCas9	ABE_NGC_20nt_3-12_020	['spCas9 NGC IBE']	Splice Site
GuideDesign3_ABE_NGC_20nt_3-12_020_-31947832_spCas9	ABE_NGC_20nt_3-12_020	['spCas9 NGC IBE']	Splice Site
GuideDesign3_ABE_NGC_20nt_3-12_020_-31950129_spCas9	ABE_NGC_20nt_3-12_020	['spCas9 NGC IBE']	Splice Site
GuideDesign3_ABE_NGC_20nt_3-12_020_-31950759_spCas9	ABE_NGC_20nt_3-12_020	['spCas9 NGC IBE']	Splice Site
GuideDesign3_ABE_NGC_20nt_3-12_020_-31950932_spCas9	ABE_NGC_20nt_3-12_020	['spCas9 NGC IBE']	Splice Site
GuideDesign3_ABE_NGC_20nt_3-12_020+_31947335_spCas9	ABE_NGC_20nt_3-12_020	['spCas9 NGC IBE']	Splice Site
GuideDesign3_ABE_NGC_20nt_3-12_020+_31947936_spCas9	ABE_NGC_20nt_3-12_020	['spCas9 NGC IBE']	Splice Site

Guide polynucleotide name	Editor	Cas9 variant	Target alteration description
GuideDesign3_ABE_NGC_20nt_3-12_020+_31949236_spCas9	ABE_NGC_20nt_3-12_020	['spCas9 NGC IBE']	Splice Site
GuideDesign3_ABE_NGC_20nt_3-12_020+_31950607_spCas9	ABE_NGC_20nt_3-12_020	['spCas9 NGC IBE']	Splice Site
GuideDesign3_ABE_NGC_20nt_3-12_020+_31950863_spCas9	ABE_NGC_20nt_3-12_020	['spCas9 NGC IBE']	Splice Site
GuideDesign3_ABE_NGC_20nt_3-12_020+_31951132_spCas9	ABE_NGC_20nt_3-12_020	['spCas9 NGC IBE']	Splice Site
GuideDesign3_ABE_NGC_20nt_3-12_020+_31951139_spCas9	ABE_NGC_20nt_3-12_020	['spCas9 NGC IBE']	Splice Site
GuideDesign3_ABE_NGC_20nt_3-12_020+_31951542_spCas9	ABE_NGC_20nt_3-12_020	['spCas9 NGC IBE']	Splice Site
GuideDesign3_ABE_NGC_20nt_3-12_020+_31951545_spCas9	ABE_NGC_20nt_3-12_020	['spCas9 NGC IBE']	Splice Site
GuideDesign3_ABE_NGC_20nt_3-12_020+_31951866_spCas9	ABE_NGC_20nt_3-12_020	['spCas9 NGC IBE']	Splice Site
GuideDesign3_ABE_NGC_20nt_3-9_008_-31946593_spCas9	ABE_NGC_20nt_3-9_008	['spCas9 NGC ABE']	Splice Site
GuideDesign3_ABE_NGC_20nt_3-9_008_-31947507_spCas9	ABE_NGC_20nt_3-9_008	['spCas9 NGC ABE']	Splice Site
GuideDesign3_ABE_NGC_20nt_3-9_008+_31947936_spCas9	ABE_NGC_20nt_3-9_008	['spCas9 NGC ABE']	Splice Site
GuideDesign3_ABE_NGC_20nt_3-9_008+_31951139_spCas9	ABE_NGC_20nt_3-9_008	['spCas9 NGC ABE']	Splice Site
GuideDesign3_ABE_NGC_20nt_3-9_008+_31951545_spCas9	ABE_NGC_20nt_3-9_008	['spCas9 NGC ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-12_018_-31946271_spCas9	ABE_NGG_20nt_3-12_018	['spCas9 IBE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-12_018_-31947508_spCas9	ABE_NGG_20nt_3-12_018	['spCas9 IBE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-12_018_-31948947_spCas9	ABE_NGG_20nt_3-12_018	['spCas9 IBE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-12_018_-31949325_spCas9	ABE_NGG_20nt_3-12_018	['spCas9 IBE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-12_018_-31949546_spCas9	ABE_NGG_20nt_3-12_018	['spCas9 IBE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-12_018_-31950130_spCas9	ABE_NGG_20nt_3-12_018	['spCas9 IBE']	Splice Site

Guide polynucleotide name	Editor	Cas9 variant	Target alteration description
GuideDesign3_ABE_NGG_20nt_3-12_018 - 31950760_spCas9	ABE_NGG_20nt_3-12_018	['spCas9 IBE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-12_018 - 31950926_spCas9	ABE_NGG_20nt_3-12_018	['spCas9 IBE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-12_018 - 31950933_spCas9	ABE_NGG_20nt_3-12_018	['spCas9 IBE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-12_018 - 31951456_spCas9	ABE_NGG_20nt_3-12_018	['spCas9 IBE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-12_018 - 31951457_spCas9	ABE_NGG_20nt_3-12_018	['spCas9 IBE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-12_018 - 31951458_spCas9	ABE_NGG_20nt_3-12_018	['spCas9 IBE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-12_018 + 31947938_spCas9	ABE_NGG_20nt_3-12_018	['spCas9 IBE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-12_018 + 31948364_spCas9	ABE_NGG_20nt_3-12_018	['spCas9 IBE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-12_018 + 31948825_spCas9	ABE_NGG_20nt_3-12_018	['spCas9 IBE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-12_018 + 31949234_spCas9	ABE_NGG_20nt_3-12_018	['spCas9 IBE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-12_018 + 31949235_spCas9	ABE_NGG_20nt_3-12_018	['spCas9 IBE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-12_018 + 31949238_spCas9	ABE_NGG_20nt_3-12_018	['spCas9 IBE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-12_018 + 31949412_spCas9	ABE_NGG_20nt_3-12_018	['spCas9 IBE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-12_018 + 31949413_spCas9	ABE_NGG_20nt_3-12_018	['spCas9 IBE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-12_018 + 31949414_spCas9	ABE_NGG_20nt_3-12_018	['spCas9 IBE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-12_018 + 31950275_spCas9	ABE_NGG_20nt_3-12_018	['spCas9 IBE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-12_018 + 31950276_spCas9	ABE_NGG_20nt_3-12_018	['spCas9 IBE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-12_018 + 31950609_spCas9	ABE_NGG_20nt_3-12_018	['spCas9 IBE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-12_018 + 31950610_spCas9	ABE_NGG_20nt_3-12_018	['spCas9 IBE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-12_018 + 31951541_spCas9	ABE_NGG_20nt_3-12_018	['spCas9 IBE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-12_018 + 31951544_spCas9	ABE_NGG_20nt_3-12_018	['spCas9 IBE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-12_018 + 31951869_spCas9	ABE_NGG_20nt_3-12_018	['spCas9 IBE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-12_018 + 31951870_spCas9	ABE_NGG_20nt_3-12_018	['spCas9 IBE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 - 31951457_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 - 31951458_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site

Guide polynucleotide name	Editor	Cas9 variant	Target alteration description
GuideDesign3_ABE_NGG_20nt_3-9_002 + 31947938_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 + 31949234_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NNNRRT_21nt_5-14_014 - 31948945_saCas9	ABE_NNNRRT_21nt_5-14_014	['saCas9 KKH ABE']	Splice Site
GuideDesign3_ABE_NNNRRT_21nt_5-14_014 - 31949323_saCas9	ABE_NNNRRT_21nt_5-14_014	['saCas9 KKH ABE']	Splice Site
GuideDesign3_ABE_NNNRRT_21nt_5-14_014 - 31950382_saCas9	ABE_NNNRRT_21nt_5-14_014	['saCas9 KKH ABE']	Splice Site
GuideDesign3_ABE_NNNRRT_21nt_5-14_014 - 31951226_saCas9	ABE_NNNRRT_21nt_5-14_014	['saCas9 KKH ABE']	Splice Site
GuideDesign3_ABE_NNNRRT_21nt_5-14_014 - 31951455_saCas9	ABE_NNNRRT_21nt_5-14_014	['saCas9 KKH ABE']	Splice Site
GuideDesign3_ABE_NNNRRT_21nt_5-14_014 + 31948361_saCas9	ABE_NNNRRT_21nt_5-14_014	['saCas9 KKH ABE']	Splice Site
GuideDesign3_ABE_NNNRRT_21nt_5-14_014 + 31949411_saCas9	ABE_NNNRRT_21nt_5-14_014	['saCas9 KKH ABE']	Splice Site
GuideDesign3_ABE_NNNRRT_21nt_5-14_014 + 31950034_saCas9	ABE_NNNRRT_21nt_5-14_014	['saCas9 KKH ABE']	Splice Site
GuideDesign3_ABE_NNNRRT_21nt_5-14_014 + 31950042_saCas9	ABE_NNNRRT_21nt_5-14_014	['saCas9 KKH ABE']	Splice Site
GuideDesign3_ABE_VTTN_22nt_5-9_017 - 31946593_cas12b	ABE_VTTN_22nt_5-9_017	['cas12b ABE']	Splice Site
GuideDesign3_ABE_VTTN_22nt_5-9_017 - 31950134_cas12b	ABE_VTTN_22nt_5-9_017	['cas12b ABE']	Splice Site
GuideDesign3_ABE_VTTN_22nt_5-9_017 - 31950390_cas12b	ABE_VTTN_22nt_5-9_017	['cas12b ABE']	Splice Site
GuideDesign3_ABE_VTTN_22nt_5-9_017 - 31951457_cas12b	ABE_VTTN_22nt_5-9_017	['cas12b ABE']	Splice Site
GuideDesign3_ABE_VTTN_22nt_5-9_017 + 31946360_cas12b	ABE_VTTN_22nt_5-9_017	['cas12b ABE']	Splice Site
GuideDesign3_ABE_VTTN_22nt_5-9_017 + 31946996_cas12b	ABE_VTTN_22nt_5-9_017	['cas12b ABE']	Splice Site
GuideDesign3_ABE_VTTN_22nt_5-9_017 + 31950037_cas12b	ABE_VTTN_22nt_5-9_017	['cas12b ABE']	Splice Site
GuideDesign3_ABE_VTTN_22nt_5-9_017 + 31950272_cas12b	ABE_VTTN_22nt_5-9_017	['cas12b ABE']	Splice Site
GuideDesign3_ABE_VTTN_22nt_5-9_017 + 31950853_cas12b	ABE_VTTN_22nt_5-9_017	['cas12b ABE']	Splice Site
GuideDesign3_ABE_VTTN_22nt_5-9_017 + 31951133_cas12b	ABE_VTTN_22nt_5-9_017	['cas12b ABE']	Splice Site

Guide polynucleotide name	Editor	Cas9 variant	Target alteration description
GuideDesign3_CBE_NNGRRT_21nt_3-12_012_-31948945_saCas9	CBE_NNGRRT_21nt_3-12_012	['saCas9 CBE']	Splice Site
GuideDesign3_CBE_NNGRRT_21nt_3-12_012_-31949323_saCas9	CBE_NNGRRT_21nt_3-12_012	['saCas9 CBE']	Splice Site
GuideDesign3_CBE_NNGRRT_21nt_3-12_012_-31950382_saCas9	CBE_NNGRRT_21nt_3-12_012	['saCas9 CBE']	Splice Site
GuideDesign3_CBE_NNGRRT_21nt_3-12_012_-31951455_saCas9	CBE_NNGRRT_21nt_3-12_012	['saCas9 CBE']	Splice Site
GuideDesign3_CBE_NNNRRT_21nt_3-12_015_-31947176_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Splice Site
GuideDesign3_CBE_NNNRRT_21nt_3-12_015_-31947927_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Splice Site
GuideDesign3_CBE_NNNRRT_21nt_3-12_015_-31948942_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Splice Site
GuideDesign3_CBE_NNNRRT_21nt_3-12_015_-31948945_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Splice Site
GuideDesign3_CBE_NNNRRT_21nt_3-12_015_-31949323_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Splice Site
GuideDesign3_CBE_NNNRRT_21nt_3-12_015_-31949397_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Splice Site
GuideDesign3_CBE_NNNRRT_21nt_3-12_015_-31950031_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Splice Site
GuideDesign3_CBE_NNNRRT_21nt_3-12_015_-31950382_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Splice Site
GuideDesign3_CBE_NNNRRT_21nt_3-12_015_-31950387_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Splice Site
GuideDesign3_CBE_NNNRRT_21nt_3-12_015_-31950925_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Splice Site
GuideDesign3_CBE_NNNRRT_21nt_3-12_015_-31950928_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Splice Site
GuideDesign3_CBE_NNNRRT_21nt_3-12_015_-31951226_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Splice Site
GuideDesign3_CBE_NNNRRT_21nt_3-12_015_-31951455_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Splice Site
GuideDesign3_CBE_NNNRRT_21nt_3-12_015_-31951856_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Splice Site

Guide polynucleotide name	Editor	Cas9 variant	Target alteration description
GuideDesign10_CBE_NGA_20nt_4-9_006_- _31946352_spCas9	CBE_NGA_20nt_4-9_006	spCas9 VRQR CBE	Splice Site
GuideDesign10_CBE_NGA_20nt_4-9_006_- _31946990_spCas9	CBE_NGA_20nt_4-9_006	spCas9 VRQR CBE	Splice Site
GuideDesign10_CBE_NGA_20nt_4-9_006_- _31947331_spCas9	CBE_NGA_20nt_4-9_006	spCas9 VRQR CBE	Splice Site
GuideDesign10_CBE_NGA_20nt_4-9_006_- _31947722_spCas9	CBE_NGA_20nt_4-9_006	spCas9 VRQR CBE	Splice Site
GuideDesign10_CBE_NGA_20nt_4-9_006_- _31950849_spCas9	CBE_NGA_20nt_4-9_006	spCas9 VRQR CBE	Splice Site
GuideDesign10_CBE_NGA_20nt_4-9_006_- _31950851_spCas9	CBE_NGA_20nt_4-9_006	spCas9 VRQR CBE	Splice Site
GuideDesign10_CBE_NGA_20nt_4-9_006_- _31951323_spCas9	CBE_NGA_20nt_4-9_006	spCas9 VRQR CBE	Splice Site
GuideDesign10_CBE_NGG_20nt_4-9_003_- _31946991_spCas9	CBE_NGG_20nt_4-9_003	spCas9 CBE	Splice Site
GuideDesign10_CBE_NGG_20nt_4-9_003_- _31949226_spCas9	CBE_NGG_20nt_4-9_003	spCas9 CBE	Splice Site
GuideDesign10_CBE_NGG_20nt_4-9_003_- _31949399_spCas9	CBE_NGG_20nt_4-9_003	spCas9 CBE	Splice Site
GuideDesign10_CBE_NGG_20nt_4-9_003_- _31949403_spCas9	CBE_NGG_20nt_4-9_003	spCas9 CBE	Splice Site
GuideDesign10_CBE_NGG_20nt_4-9_003_- _31950600_spCas9	CBE_NGG_20nt_4-9_003	spCas9 CBE	Splice Site
GuideDesign10_CBE_NGG_20nt_4-9_003_- _31950852_spCas9	CBE_NGG_20nt_4-9_003	spCas9 CBE	Splice Site
GuideDesign10_CBE_NGG_20nt_4-9_003_- _31951324_spCas9	CBE_NGG_20nt_4-9_003	spCas9 CBE	Splice Site
GuideDesign10_CBE_NGG_20nt_4-9_003_- _31951857_spCas9	CBE_NGG_20nt_4-9_003	spCas9 CBE	Splice Site
GuideDesign3_ABE_NGA_20nt_3-9_005_- _31947177_spCas9	ABE_NGA_20nt_3-9_005	['spCas9 VRQR ABE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-9_005_- _31947177_spCas9	ABE_NGA_20nt_3-9_005	['spCas9 VRQR ABE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-9_005_- _31948943_spCas9	ABE_NGA_20nt_3-9_005	['spCas9 VRQR ABE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-9_005_- _31948943_spCas9	ABE_NGA_20nt_3-9_005	['spCas9 VRQR ABE']	Splice Site

Guide polynucleotide name	Editor	Cas9 variant	Target alteration description
GuideDesign3_ABE_NGA_20nt_3-9_005_-_31949542_spCas9	ABE_NGA_20nt_3-9_005	['spCas9 VRQR ABE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-9_005_-_31949542_spCas9	ABE_NGA_20nt_3-9_005	['spCas9 VRQR ABE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-9_005_-_31950384_spCas9	ABE_NGA_20nt_3-9_005	['spCas9 VRQR ABE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-9_005_-_31950384_spCas9	ABE_NGA_20nt_3-9_005	['spCas9 VRQR ABE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-9_005_-_31950388_spCas9	ABE_NGA_20nt_3-9_005	['spCas9 VRQR ABE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-9_005_-_31950388_spCas9	ABE_NGA_20nt_3-9_005	['spCas9 VRQR ABE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-9_005_-_31951227_spCas9	ABE_NGA_20nt_3-9_005	['spCas9 VRQR ABE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-9_005_-_31951227_spCas9	ABE_NGA_20nt_3-9_005	['spCas9 VRQR ABE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-9_005_-_31951591_spCas9	ABE_NGA_20nt_3-9_005	['spCas9 VRQR ABE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-9_005_-_31951591_spCas9	ABE_NGA_20nt_3-9_005	['spCas9 VRQR ABE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-9_005+_31947000_spCas9	ABE_NGA_20nt_3-9_005	['spCas9 VRQR ABE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-9_005+_31947000_spCas9	ABE_NGA_20nt_3-9_005	['spCas9 VRQR ABE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-9_005+_31947734_spCas9	ABE_NGA_20nt_3-9_005	['spCas9 VRQR ABE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-9_005+_31947734_spCas9	ABE_NGA_20nt_3-9_005	['spCas9 VRQR ABE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-9_005+_31947939_spCas9	ABE_NGA_20nt_3-9_005	['spCas9 VRQR ABE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-9_005+_31947939_spCas9	ABE_NGA_20nt_3-9_005	['spCas9 VRQR ABE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-9_005+_31948369_spCas9	ABE_NGA_20nt_3-9_005	['spCas9 VRQR ABE']	Splice Site

Guide polynucleotide name	Editor	Cas9 variant	Target alteration description
GuideDesign3_ABE_NGA_20nt_3-9_005+_31948369_spCas9	ABE_NGA_20nt_3-9_005	['spCas9 VRQR ABE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-9_005+_31950044_spCas9	ABE_NGA_20nt_3-9_005	['spCas9 VRQR ABE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-9_005+_31950044_spCas9	ABE_NGA_20nt_3-9_005	['spCas9 VRQR ABE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-9_005+_31950277_spCas9	ABE_NGA_20nt_3-9_005	['spCas9 VRQR ABE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-9_005+_31950277_spCas9	ABE_NGA_20nt_3-9_005	['spCas9 VRQR ABE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-9_005+_31951335_spCas9	ABE_NGA_20nt_3-9_005	['spCas9 VRQR ABE']	Splice Site
GuideDesign3_ABE_NGA_20nt_3-9_005+_31951335_spCas9	ABE_NGA_20nt_3-9_005	['spCas9 VRQR ABE']	Splice Site
GuideDesign3_ABE_NGC_20nt_3-9_008_-31946270_spCas9	ABE_NGC_20nt_3-9_008	['spCas9 NGC ABE']	Splice Site
GuideDesign3_ABE_NGC_20nt_3-9_008_-31946270_spCas9	ABE_NGC_20nt_3-9_008	['spCas9 NGC ABE']	Splice Site
GuideDesign3_ABE_NGC_20nt_3-9_008_-31947173_spCas9	ABE_NGC_20nt_3-9_008	['spCas9 NGC ABE']	Splice Site
GuideDesign3_ABE_NGC_20nt_3-9_008_-31947173_spCas9	ABE_NGC_20nt_3-9_008	['spCas9 NGC ABE']	Splice Site
GuideDesign3_ABE_NGC_20nt_3-9_008_-31950129_spCas9	ABE_NGC_20nt_3-9_008	['spCas9 NGC ABE']	Splice Site
GuideDesign3_ABE_NGC_20nt_3-9_008_-31950129_spCas9	ABE_NGC_20nt_3-9_008	['spCas9 NGC ABE']	Splice Site
GuideDesign3_ABE_NGC_20nt_3-9_008_-31950759_spCas9	ABE_NGC_20nt_3-9_008	['spCas9 NGC ABE']	Splice Site
GuideDesign3_ABE_NGC_20nt_3-9_008_-31950759_spCas9	ABE_NGC_20nt_3-9_008	['spCas9 NGC ABE']	Splice Site
GuideDesign3_ABE_NGC_20nt_3-9_008+_31949236_spCas9	ABE_NGC_20nt_3-9_008	['spCas9 NGC ABE']	Splice Site
GuideDesign3_ABE_NGC_20nt_3-9_008+_31949236_spCas9	ABE_NGC_20nt_3-9_008	['spCas9 NGC ABE']	Splice Site

Guide polynucleotide name	Editor	Cas9 variant	Target alteration description
GuideDesign3_ABE_NGC_20nt_3-9_008+_31950863_spCas9	ABE_NGC_20nt_3-9_008	['spCas9 NGC ABE']	Splice Site
GuideDesign3_ABE_NGC_20nt_3-9_008+_31950863_spCas9	ABE_NGC_20nt_3-9_008	['spCas9 NGC ABE']	Splice Site
GuideDesign3_ABE_NGC_20nt_3-9_008+_31951866_spCas9	ABE_NGC_20nt_3-9_008	['spCas9 NGC ABE']	Splice Site
GuideDesign3_ABE_NGC_20nt_3-9_008+_31951866_spCas9	ABE_NGC_20nt_3-9_008	['spCas9 NGC ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 - 31946271_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 - 31946271_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 - 31947508_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 - 31947508_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 - 31948947_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 - 31948947_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 - 31949325_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 - 31949325_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 - 31950130_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 - 31950130_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 - 31950926_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 - 31950926_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 - 31951456_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 - 31951456_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 + 31948364_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 + 31948364_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 + 31948825_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 + 31948825_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 + 31949235_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site

Guide polynucleotide name	Editor	Cas9 variant	Target alteration description
GuideDesign3_ABE_NGG_20nt_3-9_002 + 31949235_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 + 31949238_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 + 31949238_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 + 31949412_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 + 31949412_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 + 31949413_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 + 31949413_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 + 31949414_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 + 31949414_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 + 31950275_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 + 31950275_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 + 31950276_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 + 31950276_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 + 31950609_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 + 31950609_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 + 31950610_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 + 31950610_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 + 31951544_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 + 31951544_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 + 31951869_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 + 31951869_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 + 31951870_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NGG_20nt_3-9_002 + 31951870_spCas9	ABE_NGG_20nt_3-9_002	['spCas9 ABE']	Splice Site
GuideDesign3_ABE_NNGRRT_21nt_5-14_011 - 31948945_saCas9	ABE_NNGRRT_21nt_5-14_011	['saCas9 ABE']	Splice Site
GuideDesign3_ABE_NNGRRT_21nt_5-14_011 - 31948945_saCas9	ABE_NNGRRT_21nt_5-14_011	['saCas9 ABE']	Splice Site

Guide polynucleotide name	Editor	Cas9 variant	Target alteration description
GuideDesign3_ABE_NNGRRT_21nt_5-14_011 - 31949323_saCas9	ABE_NNGRRT_21nt_5-14_011	['saCas9 ABE']	Splice Site
GuideDesign3_ABE_NNGRRT_21nt_5-14_011 - 31949323_saCas9	ABE_NNGRRT_21nt_5-14_011	['saCas9 ABE']	Splice Site
GuideDesign3_ABE_NNGRRT_21nt_5-14_011 - 31950382_saCas9	ABE_NNGRRT_21nt_5-14_011	['saCas9 ABE']	Splice Site
GuideDesign3_ABE_NNGRRT_21nt_5-14_011 - 31950382_saCas9	ABE_NNGRRT_21nt_5-14_011	['saCas9 ABE']	Splice Site
GuideDesign3_ABE_NNGRRT_21nt_5-14_011 - 31951455_saCas9	ABE_NNGRRT_21nt_5-14_011	['saCas9 ABE']	Splice Site
GuideDesign3_ABE_NNGRRT_21nt_5-14_011 - 31951455_saCas9	ABE_NNGRRT_21nt_5-14_011	['saCas9 ABE']	Splice Site
GuideDesign3_ABE_NNGRRT_21nt_5-14_011 + 31949411_saCas9	ABE_NNGRRT_21nt_5-14_011	['saCas9 ABE']	Splice Site
GuideDesign3_ABE_NNGRRT_21nt_5-14_011 + 31949411_saCas9	ABE_NNGRRT_21nt_5-14_011	['saCas9 ABE']	Splice Site
GuideDesign3_ABE_NNGRRT_21nt_5-14_011 + 31950042_saCas9	ABE_NNGRRT_21nt_5-14_011	['saCas9 ABE']	Splice Site
GuideDesign3_ABE_NNGRRT_21nt_5-14_011 + 31950042_saCas9	ABE_NNGRRT_21nt_5-14_011	['saCas9 ABE']	Splice Site
GuideDesign3_ABE_NNNRRT_21nt_5-14_014 - 31947176_saCas9	ABE_NNNRRT_21nt_5-14_014	['saCas9 KKH ABE']	Splice Site
GuideDesign3_ABE_NNNRRT_21nt_5-14_014 - 31947176_saCas9	ABE_NNNRRT_21nt_5-14_014	['saCas9 KKH ABE']	Splice Site
GuideDesign3_ABE_NNNRRT_21nt_5-14_014 - 31948067_saCas9	ABE_NNNRRT_21nt_5-14_014	['saCas9 KKH ABE']	Splice Site
GuideDesign3_ABE_NNNRRT_21nt_5-14_014 - 31948067_saCas9	ABE_NNNRRT_21nt_5-14_014	['saCas9 KKH ABE']	Splice Site
GuideDesign3_ABE_NNNRRT_21nt_5-14_014 - 31948499_saCas9	ABE_NNNRRT_21nt_5-14_014	['saCas9 KKH ABE']	Splice Site
GuideDesign3_ABE_NNNRRT_21nt_5-14_014 - 31948499_saCas9	ABE_NNNRRT_21nt_5-14_014	['saCas9 KKH ABE']	Splice Site
GuideDesign3_ABE_NNNRRT_21nt_5-14_014 - 31948942_saCas9	ABE_NNNRRT_21nt_5-14_014	['saCas9 KKH ABE']	Splice Site
GuideDesign3_ABE_NNNRRT_21nt_5-14_014 - 31948942_saCas9	ABE_NNNRRT_21nt_5-14_014	['saCas9 KKH ABE']	Splice Site
GuideDesign3_ABE_NNNRRT_21nt_5-14_014 - 31949545_saCas9	ABE_NNNRRT_21nt_5-14_014	['saCas9 KKH ABE']	Splice Site
GuideDesign3_ABE_NNNRRT_21nt_5-14_014 - 31949545_saCas9	ABE_NNNRRT_21nt_5-14_014	['saCas9 KKH ABE']	Splice Site

Guide polynucleotide name	Editor	Cas9 variant	Target alteration description
GuideDesign3_ABE_NNNRRT_21nt_5-14_014_-_31950135_saCas9	ABE_NNNRRT_21nt_5-14_014	['saCas9 KKH ABE']	Splice Site
GuideDesign3_ABE_NNNRRT_21nt_5-14_014_-_31950135_saCas9	ABE_NNNRRT_21nt_5-14_014	['saCas9 KKH ABE']	Splice Site
GuideDesign3_ABE_NNNRRT_21nt_5-14_014_-_31950387_saCas9	ABE_NNNRRT_21nt_5-14_014	['saCas9 KKH ABE']	Splice Site
GuideDesign3_ABE_NNNRRT_21nt_5-14_014_-_31950387_saCas9	ABE_NNNRRT_21nt_5-14_014	['saCas9 KKH ABE']	Splice Site
GuideDesign3_ABE_NNNRRT_21nt_5-14_014_-_31950925_saCas9	ABE_NNNRRT_21nt_5-14_014	['saCas9 KKH ABE']	Splice Site
GuideDesign3_ABE_NNNRRT_21nt_5-14_014_-_31950925_saCas9	ABE_NNNRRT_21nt_5-14_014	['saCas9 KKH ABE']	Splice Site
GuideDesign3_ABE_NNNRRT_21nt_5-14_014_-_31950928_saCas9	ABE_NNNRRT_21nt_5-14_014	['saCas9 KKH ABE']	Splice Site
GuideDesign3_ABE_NNNRRT_21nt_5-14_014_-_31950928_saCas9	ABE_NNNRRT_21nt_5-14_014	['saCas9 KKH ABE']	Splice Site
GuideDesign3_ABE_NNNRRT_21nt_5-14_014_+_31946366_saCas9	ABE_NNNRRT_21nt_5-14_014	['saCas9 KKH ABE']	Splice Site
GuideDesign3_ABE_NNNRRT_21nt_5-14_014_+_31946366_saCas9	ABE_NNNRRT_21nt_5-14_014	['saCas9 KKH ABE']	Splice Site
GuideDesign3_ABE_NNNRRT_21nt_5-14_014_+_31948817_saCas9	ABE_NNNRRT_21nt_5-14_014	['saCas9 KKH ABE']	Splice Site
GuideDesign3_ABE_NNNRRT_21nt_5-14_014_+_31948817_saCas9	ABE_NNNRRT_21nt_5-14_014	['saCas9 KKH ABE']	Splice Site
GuideDesign3_ABE_NNNRRT_21nt_5-14_014_+_31951334_saCas9	ABE_NNNRRT_21nt_5-14_014	['saCas9 KKH ABE']	Splice Site
GuideDesign3_ABE_NNNRRT_21nt_5-14_014_+_31951334_saCas9	ABE_NNNRRT_21nt_5-14_014	['saCas9 KKH ABE']	Splice Site
GuideDesign3_CBE_NNGRRT_21nt_3-12_012_-_31947927_saCas9	CBE_NNGRRT_21nt_3-12_012	['saCas9 CBE']	Splice Site
GuideDesign3_CBE_NNGRRT_21nt_3-12_012_-_31947927_saCas9	CBE_NNGRRT_21nt_3-12_012	['saCas9 CBE']	Splice Site
GuideDesign3_CBE_NNGRRT_21nt_3-12_012_-_31949397_saCas9	CBE_NNGRRT_21nt_3-12_012	['saCas9 CBE']	Splice Site
GuideDesign3_CBE_NNGRRT_21nt_3-12_012_-_31949397_saCas9	CBE_NNGRRT_21nt_3-12_012	['saCas9 CBE']	Splice Site

Guide polynucleotide name	Editor	Cas9 variant	Target alteration description
GuideDesign3_CBE_NNGRRT_21nt_3-12_012 - 31950031_saCas9	CBE_NNGRRT_21nt_3-12_012	['saCas9 CBE']	Splice Site
GuideDesign3_CBE_NNGRRT_21nt_3-12_012 - 31950031_saCas9	CBE_NNGRRT_21nt_3-12_012	['saCas9 CBE']	Splice Site
GuideDesign3_CBE_NNGRRT_21nt_3-12_012 - 31951856_saCas9	CBE_NNGRRT_21nt_3-12_012	['saCas9 CBE']	Splice Site
GuideDesign3_CBE_NNGRRT_21nt_3-12_012 - 31951856_saCas9	CBE_NNGRRT_21nt_3-12_012	['saCas9 CBE']	Splice Site
GuideDesign3_CBE_NNNRRT_21nt_3-12_015 - 31946263_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Splice Site
GuideDesign3_CBE_NNNRRT_21nt_3-12_015 - 31946263_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Splice Site
GuideDesign3_CBE_NNNRRT_21nt_3-12_015 - 31946354_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Splice Site
GuideDesign3_CBE_NNNRRT_21nt_3-12_015 - 31946354_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Splice Site
GuideDesign3_CBE_NNNRRT_21nt_3-12_015 - 31946985_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Splice Site
GuideDesign3_CBE_NNNRRT_21nt_3-12_015 - 31946985_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Splice Site
GuideDesign3_CBE_NNNRRT_21nt_3-12_015 - 31947322_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Splice Site
GuideDesign3_CBE_NNNRRT_21nt_3-12_015 - 31947322_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Splice Site
GuideDesign3_CBE_NNNRRT_21nt_3-12_015 - 31947719_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Splice Site
GuideDesign3_CBE_NNNRRT_21nt_3-12_015 - 31947719_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Splice Site
GuideDesign3_CBE_NNNRRT_21nt_3-12_015 - 31947724_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Splice Site
GuideDesign3_CBE_NNNRRT_21nt_3-12_015 - 31947724_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Splice Site
GuideDesign3_CBE_NNNRRT_21nt_3-12_015 - 31950269_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Splice Site
GuideDesign3_CBE_NNNRRT_21nt_3-12_015 - 31950269_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Splice Site

Guide polynucleotide name	Editor	Cas9 variant	Target alteration description
GuideDesign3_CBE_NNNRRT_21nt_3-12_015_-_31950599_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Splice Site
GuideDesign3_CBE_NNNRRT_21nt_3-12_015_-_31950599_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Splice Site
GuideDesign3_CBE_NNNRRT_21nt_3-12_015_-_31950922_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Splice Site
GuideDesign3_CBE_NNNRRT_21nt_3-12_015_-_31950922_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Splice Site
GuideDesign10_CBE_NGC_20nt_4-9_009_-_31947141_spCas9	CBE_NGC_20nt_4-9_009	spCas9 NGC CBE	Stop Codon
GuideDesign10_CBE_NGC_20nt_4-9_009_-_31948418_spCas9	CBE_NGC_20nt_4-9_009	spCas9 NGC CBE	Stop Codon
GuideDesign10_CBE_NGC_20nt_4-9_009_-_31948461_spCas9	CBE_NGC_20nt_4-9_009	spCas9 NGC CBE	Stop Codon
GuideDesign10_CBE_NGC_20nt_4-9_009_+_31946572_spCas9	CBE_NGC_20nt_4-9_009	spCas9 NGC CBE	Stop Codon
GuideDesign10_CBE_NGC_20nt_4-9_009_+_31947152_spCas9	CBE_NGC_20nt_4-9_009	spCas9 NGC CBE	Stop Codon
GuideDesign10_CBE_NGC_20nt_4-9_009_+_31947758_spCas9	CBE_NGC_20nt_4-9_009	spCas9 NGC CBE	Stop Codon
GuideDesign10_CBE_NGC_20nt_4-9_009_+_31948862_spCas9	CBE_NGC_20nt_4-9_009	spCas9 NGC CBE	Stop Codon
GuideDesign10_CBE_NGC_20nt_4-9_009_+_31950757_spCas9	CBE_NGC_20nt_4-9_009	spCas9 NGC CBE	Stop Codon
GuideDesign10_CBE_NGC_20nt_4-9_009_+_31950937_spCas9	CBE_NGC_20nt_4-9_009	spCas9 NGC CBE	Stop Codon
GuideDesign10_CBE_NGC_20nt_4-9_009_+_31951925_spCas9	CBE_NGC_20nt_4-9_009	spCas9 NGC CBE	Stop Codon
GuideDesign10_CBE_NGC_20nt_4-9_009_+_31951966_spCas9	CBE_NGC_20nt_4-9_009	spCas9 NGC CBE	Stop Codon
GuideDesign3_CBE_NNGRRT_21nt_3-12_012_+_31951994_saCas9	CBE_NNGRRT_21nt_3-12_012	['saCas9 CBE']	Stop Codon
GuideDesign3_CBE_NNNRRT_21nt_3-12_015_-_31950102_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Stop Codon

Guide polynucleotide name	Editor	Cas9 variant	Target alteration description
GuideDesign3_CBE_NNNRRT_21nt_3-12_015+_31946459_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Stop Codon
GuideDesign3_CBE_NNNRRT_21nt_3-12_015+_31946513_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Stop Codon
GuideDesign3_CBE_NNNRRT_21nt_3-12_015+_31946573_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Stop Codon
GuideDesign3_CBE_NNNRRT_21nt_3-12_015+_31947137_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Stop Codon
GuideDesign3_CBE_NNNRRT_21nt_3-12_015+_31949486_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Stop Codon
GuideDesign3_CBE_NNNRRT_21nt_3-12_015+_31949493_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Stop Codon
GuideDesign3_CBE_NNNRRT_21nt_3-12_015+_31950110_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Stop Codon
GuideDesign3_CBE_NNNRRT_21nt_3-12_015+_31951909_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Stop Codon
GuideDesign3_CBE_NNNRRT_21nt_3-12_015+_31951994_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Stop Codon
GuideDesign10_CBE_NGA_20nt_4-9_006_-31946539_spCas9	CBE_NGA_20nt_4-9_006	spCas9 VRQR CBE	Stop Codon
GuideDesign10_CBE_NGA_20nt_4-9_006_-31947033_spCas9	CBE_NGA_20nt_4-9_006	spCas9 VRQR CBE	Stop Codon
GuideDesign10_CBE_NGA_20nt_4-9_006_-31947477_spCas9	CBE_NGA_20nt_4-9_006	spCas9 VRQR CBE	Stop Codon
GuideDesign10_CBE_NGA_20nt_4-9_006_-31948907_spCas9	CBE_NGA_20nt_4-9_006	spCas9 VRQR CBE	Stop Codon
GuideDesign10_CBE_NGA_20nt_4-9_006_-31950068_spCas9	CBE_NGA_20nt_4-9_006	spCas9 VRQR CBE	Stop Codon
GuideDesign10_CBE_NGA_20nt_4-9_006_-31950070_spCas9	CBE_NGA_20nt_4-9_006	spCas9 VRQR CBE	Stop Codon
GuideDesign10_CBE_NGA_20nt_4-9_006_-31951968_spCas9	CBE_NGA_20nt_4-9_006	spCas9 VRQR CBE	Stop Codon
GuideDesign10_CBE_NGA_20nt_4-9_006_-31951972_spCas9	CBE_NGA_20nt_4-9_006	spCas9 VRQR CBE	Stop Codon

Guide polynucleotide name	Editor	Cas9 variant	Target alteration description
GuideDesign10_CBE_NGA_20nt_4-9_006+_31946404_spCas9	CBE_NGA_20nt_4-9_006	spCas9 VRQR CBE	Stop Codon
GuideDesign10_CBE_NGA_20nt_4-9_006+_31946568_spCas9	CBE_NGA_20nt_4-9_006	spCas9 VRQR CBE	Stop Codon
GuideDesign10_CBE_NGA_20nt_4-9_006+_31947135_spCas9	CBE_NGA_20nt_4-9_006	spCas9 VRQR CBE	Stop Codon
GuideDesign10_CBE_NGA_20nt_4-9_006+_31947139_spCas9	CBE_NGA_20nt_4-9_006	spCas9 VRQR CBE	Stop Codon
GuideDesign10_CBE_NGA_20nt_4-9_006+_31947148_spCas9	CBE_NGA_20nt_4-9_006	spCas9 VRQR CBE	Stop Codon
GuideDesign10_CBE_NGA_20nt_4-9_006+_31947161_spCas9	CBE_NGA_20nt_4-9_006	spCas9 VRQR CBE	Stop Codon
GuideDesign10_CBE_NGA_20nt_4-9_006+_31947394_spCas9	CBE_NGA_20nt_4-9_006	spCas9 VRQR CBE	Stop Codon
GuideDesign10_CBE_NGA_20nt_4-9_006+_31947460_spCas9	CBE_NGA_20nt_4-9_006	spCas9 VRQR CBE	Stop Codon
GuideDesign10_CBE_NGA_20nt_4-9_006+_31947474_spCas9	CBE_NGA_20nt_4-9_006	spCas9 VRQR CBE	Stop Codon
GuideDesign10_CBE_NGA_20nt_4-9_006+_31947942_spCas9	CBE_NGA_20nt_4-9_006	spCas9 VRQR CBE	Stop Codon
GuideDesign10_CBE_NGA_20nt_4-9_006+_31948866_spCas9	CBE_NGA_20nt_4-9_006	spCas9 VRQR CBE	Stop Codon
GuideDesign10_CBE_NGA_20nt_4-9_006+_31949541_spCas9	CBE_NGA_20nt_4-9_006	spCas9 VRQR CBE	Stop Codon
GuideDesign10_CBE_NGA_20nt_4-9_006+_31949543_spCas9	CBE_NGA_20nt_4-9_006	spCas9 VRQR CBE	Stop Codon
GuideDesign10_CBE_NGA_20nt_4-9_006+_31950113_spCas9	CBE_NGA_20nt_4-9_006	spCas9 VRQR CBE	Stop Codon
GuideDesign10_CBE_NGA_20nt_4-9_006+_31950755_spCas9	CBE_NGA_20nt_4-9_006	spCas9 VRQR CBE	Stop Codon
GuideDesign10_CBE_NGA_20nt_4-9_006+_31950927_spCas9	CBE_NGA_20nt_4-9_006	spCas9 VRQR CBE	Stop Codon
GuideDesign10_CBE_NGA_20nt_4-9_006+_31951361_spCas9	CBE_NGA_20nt_4-9_006	spCas9 VRQR CBE	Stop Codon

Guide polynucleotide name	Editor	Cas9 variant	Target alteration description
GuideDesign10_CBE_NGA_20nt_4-9_006+_31951969_spCas9	CBE_NGA_20nt_4-9_006	spCas9 VRQR CBE	Stop Codon
GuideDesign10_CBE_NGG_20nt_4-9_003 - 31947142_spCas9	CBE_NGG_20nt_4-9_003	spCas9 CBE	Stop Codon
GuideDesign10_CBE_NGG_20nt_4-9_003 - 31948419_spCas9	CBE_NGG_20nt_4-9_003	spCas9 CBE	Stop Codon
GuideDesign10_CBE_NGG_20nt_4-9_003 - 31948908_spCas9	CBE_NGG_20nt_4-9_003	spCas9 CBE	Stop Codon
GuideDesign10_CBE_NGG_20nt_4-9_003 - 31948909_spCas9	CBE_NGG_20nt_4-9_003	spCas9 CBE	Stop Codon
GuideDesign10_CBE_NGG_20nt_4-9_003 - 31950110_spCas9	CBE_NGG_20nt_4-9_003	spCas9 CBE	Stop Codon
GuideDesign10_CBE_NGG_20nt_4-9_003 + 31946448_spCas9	CBE_NGG_20nt_4-9_003	spCas9 CBE	Stop Codon
GuideDesign10_CBE_NGG_20nt_4-9_003 + 31946449_spCas9	CBE_NGG_20nt_4-9_003	spCas9 CBE	Stop Codon
GuideDesign10_CBE_NGG_20nt_4-9_003 + 31946460_spCas9	CBE_NGG_20nt_4-9_003	spCas9 CBE	Stop Codon
GuideDesign10_CBE_NGG_20nt_4-9_003 + 31946567_spCas9	CBE_NGG_20nt_4-9_003	spCas9 CBE	Stop Codon
GuideDesign10_CBE_NGG_20nt_4-9_003 + 31946571_spCas9	CBE_NGG_20nt_4-9_003	spCas9 CBE	Stop Codon
GuideDesign10_CBE_NGG_20nt_4-9_003 + 31947138_spCas9	CBE_NGG_20nt_4-9_003	spCas9 CBE	Stop Codon
GuideDesign10_CBE_NGG_20nt_4-9_003 + 31947459_spCas9	CBE_NGG_20nt_4-9_003	spCas9 CBE	Stop Codon
GuideDesign10_CBE_NGG_20nt_4-9_003 + 31947463_spCas9	CBE_NGG_20nt_4-9_003	spCas9 CBE	Stop Codon
GuideDesign10_CBE_NGG_20nt_4-9_003 + 31947466_spCas9	CBE_NGG_20nt_4-9_003	spCas9 CBE	Stop Codon
GuideDesign10_CBE_NGG_20nt_4-9_003 + 31947473_spCas9	CBE_NGG_20nt_4-9_003	spCas9 CBE	Stop Codon
GuideDesign10_CBE_NGG_20nt_4-9_003 + 31949539_spCas9	CBE_NGG_20nt_4-9_003	spCas9 CBE	Stop Codon
GuideDesign10_CBE_NGG_20nt_4-9_003 + 31949540_spCas9	CBE_NGG_20nt_4-9_003	spCas9 CBE	Stop Codon
GuideDesign10_CBE_NGG_20nt_4-9_003 + 31950936_spCas9	CBE_NGG_20nt_4-9_003	spCas9 CBE	Stop Codon
GuideDesign10_CBE_NGG_20nt_4-9_003 + 31951965_spCas9	CBE_NGG_20nt_4-9_003	spCas9 CBE	Stop Codon
GuideDesign10_CBE_NGG_20nt_4-9_003 + 31951996_spCas9	CBE_NGG_20nt_4-9_003	spCas9 CBE	Stop Codon
GuideDesign10_CBE_NGG_20nt_4-9_003 + 31951997_spCas9	CBE_NGG_20nt_4-9_003	spCas9 CBE	Stop Codon
GuideDesign3_CBE_NNGRRT_21nt_3-12_012 + 31946459_saCas9	CBE_NNGRRT_21nt_3-12_012	['saCas9 CBE']	Stop Codon
GuideDesign3_CBE_NNGRRT_21nt_3-12_012 + 31946459_saCas9	CBE_NNGRRT_21nt_3-12_012	['saCas9 CBE']	Stop Codon
GuideDesign3_CBE_NNGRRT_21nt_3-12_012 + 31946573_saCas9	CBE_NNGRRT_21nt_3-12_012	['saCas9 CBE']	Stop Codon

Guide polynucleotide name	Editor	Cas9 variant	Target alteration description
GuideDesign3_CBE_NNGRRT_21nt_3-12_012 + 31946573_saCas9	CBE_NNGRRT_21nt_3-12_012	['saCas9 CBE']	Stop Codon
GuideDesign3_CBE_NNGRRT_21nt_3-12_012 + 31947137_saCas9	CBE_NNGRRT_21nt_3-12_012	['saCas9 CBE']	Stop Codon
GuideDesign3_CBE_NNGRRT_21nt_3-12_012 + 31947137_saCas9	CBE_NNGRRT_21nt_3-12_012	['saCas9 CBE']	Stop Codon
GuideDesign3_CBE_NNGRRT_21nt_3-12_012 + 31949493_saCas9	CBE_NNGRRT_21nt_3-12_012	['saCas9 CBE']	Stop Codon
GuideDesign3_CBE_NNGRRT_21nt_3-12_012 + 31949493_saCas9	CBE_NNGRRT_21nt_3-12_012	['saCas9 CBE']	Stop Codon
GuideDesign3_CBE_NNNRRT_21nt_3-12_015 - 31946530_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Stop Codon
GuideDesign3_CBE_NNNRRT_21nt_3-12_015 - 31946530_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Stop Codon
GuideDesign3_CBE_NNNRRT_21nt_3-12_015 - 31946538_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Stop Codon
GuideDesign3_CBE_NNNRRT_21nt_3-12_015 - 31946538_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Stop Codon
GuideDesign3_CBE_NNNRRT_21nt_3-12_015 - 31947030_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Stop Codon
GuideDesign3_CBE_NNNRRT_21nt_3-12_015 - 31947030_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Stop Codon
GuideDesign3_CBE_NNNRRT_21nt_3-12_015 - 31947137_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Stop Codon
GuideDesign3_CBE_NNNRRT_21nt_3-12_015 - 31947137_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Stop Codon
GuideDesign3_CBE_NNNRRT_21nt_3-12_015 - 31950106_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Stop Codon
GuideDesign3_CBE_NNNRRT_21nt_3-12_015 - 31950106_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Stop Codon
GuideDesign3_CBE_NNNRRT_21nt_3-12_015 - 31950109_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Stop Codon
GuideDesign3_CBE_NNNRRT_21nt_3-12_015 - 31950109_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Stop Codon
GuideDesign3_CBE_NNNRRT_21nt_3-12_015 - 31951965_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Stop Codon

Guide polynucleotide name	Editor	Cas9 variant	Target alteration description
GuideDesign3_CBE_NNNRRT_21nt_3-12_015_-_31951965_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Stop Codon
GuideDesign3_CBE_NNNRRT_21nt_3-12_015_+_31947132_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Stop Codon
GuideDesign3_CBE_NNNRRT_21nt_3-12_015_+_31947132_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Stop Codon
GuideDesign3_CBE_NNNRRT_21nt_3-12_015_+_31947151_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Stop Codon
GuideDesign3_CBE_NNNRRT_21nt_3-12_015_+_31947151_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Stop Codon
GuideDesign3_CBE_NNNRRT_21nt_3-12_015_+_31947460_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Stop Codon
GuideDesign3_CBE_NNNRRT_21nt_3-12_015_+_31947460_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Stop Codon
GuideDesign3_CBE_NNNRRT_21nt_3-12_015_+_31947939_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Stop Codon
GuideDesign3_CBE_NNNRRT_21nt_3-12_015_+_31947939_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Stop Codon
GuideDesign3_CBE_NNNRRT_21nt_3-12_015_+_31948478_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Stop Codon
GuideDesign3_CBE_NNNRRT_21nt_3-12_015_+_31948478_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Stop Codon
GuideDesign3_CBE_NNNRRT_21nt_3-12_015_+_31948863_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Stop Codon
GuideDesign3_CBE_NNNRRT_21nt_3-12_015_+_31948863_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Stop Codon
GuideDesign3_CBE_NNNRRT_21nt_3-12_015_+_31949540_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Stop Codon
GuideDesign3_CBE_NNNRRT_21nt_3-12_015_+_31949540_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Stop Codon
GuideDesign3_CBE_NNNRRT_21nt_3-12_015_+_31950116_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Stop Codon
GuideDesign3_CBE_NNNRRT_21nt_3-12_015_+_31950116_saCas9	CBE_NNNRRT_21nt_3-12_015	['saCas9 KKH CBE']	Stop Codon

Table 2C (CONTINUED).

Guide polynucleotide name	Target sequence	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
GuideDesign10_CBE_NGA_20nt_4-9_006_-31947177_spCas9	CTTCTCACCTCCGTTGT CACAGA	2055	CUUCUCACCUCCGU UGUCAC	2463	AGA
GuideDesign10_CBE_NGA_20nt_4-9_006_-31948943_spCas9	CTGACCATCAGTCATGA GGATGA	2056	CUGACCAUCAGUCA UGAGGA	2464	TGA
GuideDesign10_CBE_NGA_20nt_4-9_006_-31949542_spCas9	CTCCCTACCGATCATTT GGTAGA	2057	CUCCCUACCGAUCA UUUGGU	2465	AGA
GuideDesign10_CBE_NGA_20nt_4-9_006_-31950384_spCas9	TTACCTACGCTGACCTT GATTGA	2058	UUACCUACGCUGAC CUUGAU	2466	TGA
GuideDesign10_CBE_NGA_20nt_4-9_006_-31950388_spCas9	ATCCTTACCTACGCTGA CCTTGA	2059	AUCCUUACCUACGC UGACCU	2467	TGA
GuideDesign10_CBE_NGA_20nt_4-9_006_-31951227_spCas9	TCTCACCTTATCCCCAT TCTTGA	2060	UCUCACCUUAUCCC CAUUCU	2468	TGA
GuideDesign10_CBE_NGC_20nt_4-9_009_-31946270_spCas9	TCGCTTACCTCCAGACA AGAGGC	2061	UCGCUUACCUCCAG ACAAGA	2469	GGC
GuideDesign10_CBE_NGC_20nt_4-9_009_-31947173_spCas9	TCACCTCCGTTGTCACA GATCGC	2062	UCACCUCCGUUGUC ACAGAU	2470	CGC
GuideDesign10_CBE_NGC_20nt_4-9_009_-31950129_spCas9	CTTACAATGACTGAGAT CTTGGC	2063	CUUACAAUGACUGA GAUCUU	2471	GGC
GuideDesign10_CBE_NGC_20nt_4-9_009_-31951854_spCas9	AACCTGCAGAGGCAGTG GGGTGC	2064	AACCUGCAGAGGCA GUGGGG	2472	TGC
GuideDesign10_CBE_NGG_20nt_4-9_003_-31946271_spCas9	CTCGCTTACCTCCAGAC AAGAGG	2065	CUCGCUUACCUCCA GACAAG	2473	AGG
GuideDesign10_CBE_NGG_20nt_4-9_003_-31948947_spCas9	CCTTCTGACCATCAGTC ATGAGG	2066	CCUUCUGACCAUCA GUCAUG	2474	AGG
GuideDesign10_CBE_NGG_20nt_4-9_003_-31949325_spCas9	TCACCCAGATAATCCTC CCTTGG	2067	UCACCCAGAUAAUC CUCCCU	2475	TGG
GuideDesign10_CBE_NGG_20nt_4-9_003_-31950130_spCas9	GCTTACAATGACTGAGA TCTTGG	2068	GCUUACAAUGACUG AGAUCU	2476	TGG
GuideDesign10_CBE_NGG_20nt_4-9_003_-31950926_spCas9	CTTACTTTGTTGCTGGC AAGTGG	2069	CUUACUUUGUUGCU GGCAAG	2477	TGG

Guide polynucleotide name	Target sequence	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
GuideDesign10_CBE_N GG_20nt_4-9_003_- 31951456_spCas9	TCTCACCTCTGCAAGTA TTGGGG	2070	UCUCACCUCUGCAA GUAUUG	2478	GGG
GuideDesign3_ABE_N GA_20nt_3-12_019_- 31946273_spCas9	CCCTCGCTTACCTCCAG ACAAGA	2071	CCCUCGCUUACCUC CAGACA	2479	AGA
GuideDesign3_ABE_N GA_20nt_3-12_019_- 31947177_spCas9	CTTCTCACCTCCGTTGT CACAGA	2072	CUUCUCACCUCCGU UGUCAC	2480	AGA
GuideDesign3_ABE_N GA_20nt_3-12_019_- 31947511_spCas9	GGTCAAAGGTCACCTTG GCAGGA	2073	GGUCAAGGUCACC UUGGCA	2481	GGA
GuideDesign3_ABE_N GA_20nt_3-12_019_- 31948064_spCas9	TTCCACCTTCTCAATTA AGTTGA	2074	UCCACCUUCUCAA UUAAGU	2482	TGA
GuideDesign3_ABE_N GA_20nt_3-12_019_- 31948500_spCas9	TAACCTCTGACCTTCAT AATTGA	2075	UAACCUCUGACCUU CAUAAU	2483	TGA
GuideDesign3_ABE_N GA_20nt_3-12_019_- 31948943_spCas9	CTGACCATCAGTCATGA GGATGA	2076	CUGACCAUCAGUCA UGAGGA	2484	TGA
GuideDesign3_ABE_N GA_20nt_3-12_019_- 31948946_spCas9	CTTCTGACCATCAGTCA TGAGGA	2077	CUUCUGACCAUCAG UCAUGA	2485	GGA
GuideDesign3_ABE_N GA_20nt_3-12_019_- 31948949_spCas9	TCCCTTCTGACCATCAG TCATGA	2078	UCCCUUCUGACCAU CAGUCA	2486	TGA
GuideDesign3_ABE_N GA_20nt_3-12_019_- 31949542_spCas9	CTCCCTACCGATCATTT GGTAGA	2079	CUCCCUACCGAUC UUUGGU	2487	AGA
GuideDesign3_ABE_N GA_20nt_3-12_019_- 31950136_spCas9	TTCTGTGCTTACAATGA CTGAGA	2080	UUCUGUGCUUACAA UGACUG	2488	AGA
GuideDesign3_ABE_N GA_20nt_3-12_019_- 31950384_spCas9	TTACCTACGCTGACCTT GATTGA	2081	UUACCUACGCUGAC CUUGAU	2489	TGA
GuideDesign3_ABE_N GA_20nt_3-12_019_- 31950388_spCas9	ATCCTTACCTACGCTGA CCTTGA	2082	AUCCUUACCUACGC UGACCU	2490	TGA
GuideDesign3_ABE_N GA_20nt_3-12_019_- 31951227_spCas9	TCTCACCTTATCCCCAT TCTTGA	2083	UCUCACCUUAUCCC CAUUCU	2491	TGA
GuideDesign3_ABE_N GA_20nt_3-12_019_- 31951591_spCas9	GAGGACTCACTTGAATG AAACGA	2084	GAGGACUCACUUGA AUGAAA	2492	CGA
GuideDesign3_ABE_N GA_20nt_3- 12_019_+_31947000_sp Cas9	TCAAAGCAATCCACTGT CCAAGA	2085	UCAAAGCAAUCCAC UGUCCA	2493	AGA
GuideDesign3_ABE_N GA_20nt_3-	CTCCCAGACTCCTTCAT GTACGA	2086	CUCCAGACUCCUU CAUGUA	2494	CGA

Guide polynucleotide name	Target sequence	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
12_019+_31947734_sp Cas9					
GuideDesign3_ABE_N GA_20nt_3- 12_019+_31947933_sp Cas9	CTGGCACCCAGGGGAAC AACAGA	2087	CUGGCACCCAGGGG AACAAC	2495	AGA
GuideDesign3_ABE_N GA_20nt_3- 12_019+_31947939_sp Cas9	CCCAGGGGAACAACAGA AGCGGA	2088	CCCAGGGGAACAAC AGAAGC	2496	GGA
GuideDesign3_ABE_N GA_20nt_3- 12_019+_31948369_sp Cas9	ACAGGTGGCAAGTTATG GTGTGA	2089	ACAGGUGGCAAGUU AUGGUG	2497	TGA
GuideDesign3_ABE_N GA_20nt_3- 12_019+_31948818_sp Cas9	CCTCTCCACAGACCACA AGTTGA	2090	CCUCUCCACAGACC ACAAGU	2498	TGA
GuideDesign3_ABE_N GA_20nt_3- 12_019+_31950044_sp Cas9	GCCAGATGAAAGCCAGT CTCTGA	2091	GCCAGAUGAAAGCC AGUCUC	2499	TGA
GuideDesign3_ABE_N GA_20nt_3- 12_019+_31950277_sp Cas9	GTCCCCAGCGCCCTTCA AAGGGA	2092	GUCCCCAGCGCCCU UCAAG	2500	GGA
GuideDesign3_ABE_N GA_20nt_3- 12_019+_31950611_sp Cas9	ACTTCAGGAGGGGAGAA GCGGGA	2093	ACUUCAGGAGGGGA GAAGCG	2501	GGA
GuideDesign3_ABE_N GA_20nt_3- 12_019+_31951331_sp Cas9	CCCCTACAGAAAGGCAG CTGTGA	2094	CCCCUACAGAAAGG CAGCUG	2502	TGA
GuideDesign3_ABE_N GA_20nt_3- 12_019+_31951333_sp Cas9	CCTACAGAAAGGCAGCT GTGAGA	2095	CCUACAGAAAGGCA GCUGUG	2503	AGA
GuideDesign3_ABE_N GA_20nt_3- 12_019+_31951335_sp Cas9	TACAGAAAGGCAGCTGT GAGAGA	2096	UACAGAAAGGCAGC UGUGAG	2504	AGA
GuideDesign3_ABE_N GA_20nt_3-9_005_- 31948064_spCas9	TTCCACCTTCTCAATTA AGTTGA	2097	UCCACCUUCUCAA UUAAGU	2505	TGA
GuideDesign3_ABE_N GA_20nt_3-9_005_- 31948946_spCas9	CTTCTGACCATCAGTCA TGAGGA	2098	CUUCUGACCAUCAG UCAUGA	2506	GGA
GuideDesign3_ABE_N GA_20nt_3-	ACTTCAGGAGGGGAGAA GCGGGA	2099	ACUUCAGGAGGGGA GAAGCG	2507	GGA

Guide polynucleotide name	Target sequence	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
9_005_+_31950611_spCas9					
GuideDesign3_ABE_NGA_20nt_3-9_005_+_31951331_spCas9	CCCCTACAGAAAGGCAGCTGTGA	2100	CCCCUACAGAAAGGCAGCUG	2508	TGA
GuideDesign3_ABE_NGA_20nt_3-9_005_+_31951333_spCas9	CCTACAGAAAGGCAGCTGTGAGA	2101	CCUACAGAAAGGCAGCUGUG	2509	AGA
GuideDesign3_ABE_NGC_20nt_3-12_020_-31946270_spCas9	TCGCTTACCTCCAGACAAGAGGC	2102	UCGCUUACCUCCAGACAAGA	2510	GGC
GuideDesign3_ABE_NGC_20nt_3-12_020_-31946593_spCas9	GCCCTCAAACCTCTGCACTCTGC	2103	GCCCUCAAACCUCUGCACUC	2511	TGC
GuideDesign3_ABE_NGC_20nt_3-12_020_-31947173_spCas9	TCACCTCCGTTGTCACAGATCGC	2104	UCACCUCCGUUGUCACAGAU	2512	CGC
GuideDesign3_ABE_NGC_20nt_3-12_020_-31947507_spCas9	AAAGGTCACCTTGGCAGGAAGGC	2105	AAAGGUCACCUUGGCAGGAA	2513	GGC
GuideDesign3_ABE_NGC_20nt_3-12_020_-31947832_spCas9	CTGTCTTCAAACCTGGGCCGTGC	2106	CUGUCUCAAACCUGGGCCG	2514	TGC
GuideDesign3_ABE_NGC_20nt_3-12_020_-31950129_spCas9	CTTACAATGACTGAGATCTTGGC	2107	CUUACAAUGACUGA GAUCUU	2515	GGC
GuideDesign3_ABE_NGC_20nt_3-12_020_-31950759_spCas9	ACGCTCTCACCTGATAGTCTGGC	2108	ACGCUCUCACCUGA UAGUCU	2516	GGC
GuideDesign3_ABE_NGC_20nt_3-12_020_-31950932_spCas9	GTATGTCTTACTTTGTTGCTGGC	2109	GUAUGUCUUACUUU GUUGCU	2517	GGC
GuideDesign3_ABE_NGC_20nt_3-12_020_+_31947335_spCas9	ATACCTCTGCAGCGGGGTACTGC	2110	AUACCUCUGCAGCGGGGUAC	2518	TGC
GuideDesign3_ABE_NGC_20nt_3-12_020_+_31947936_spCas9	GCACCCAGGGGAACAACAGAAGC	2111	GCACCCAGGGGAACAACAGA	2519	AGC
GuideDesign3_ABE_NGC_20nt_3-12_020_+_31949236_spCas9	CTGCAGGATTGCACAACATGGGC	2112	CUGCAGGAUUGCACAACAUG	2520	GGC
GuideDesign3_ABE_NGC_20nt_3-12_020_+_31950607_spCas9	TCCTACTTCAGGAGGGGAGAAGC	2113	UCCUACUUCAGGAGGGGAGA	2521	AGC

Guide polynucleotide name	Target sequence	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
GuideDesign3_ABE_N GC_20nt_3- 12_020+_31950863_sp Cas9	ATAGGCCCATTTGTCTC CCCTGC	2114	AUAGGCCCAUUUGU CUCCCC	2522	TGC
GuideDesign3_ABE_N GC_20nt_3- 12_020+_31951132_sp Cas9	TATTCGTCCAGAGGAAG AGCTGC	2115	UAUUCGUCCAGAGG AAGAGC	2523	TGC
GuideDesign3_ABE_N GC_20nt_3- 12_020+_31951139_sp Cas9	CCAGAGGAAGAGCTGCT CCCTGC	2116	CCAGAGGAAGAGCU GCUCCC	2524	TGC
GuideDesign3_ABE_N GC_20nt_3- 12_020+_31951542_sp Cas9	CTCTCCTTGCAGGTGAT TCTGGC	2117	CUCUCCUUGCAGGU GAUUCU	2525	GGC
GuideDesign3_ABE_N GC_20nt_3- 12_020+_31951545_sp Cas9	TCCTTGCAGGTGATTCT GGCGGC	2118	UCCUUGCAGGUGAU UCUGGC	2526	GGC
GuideDesign3_ABE_N GC_20nt_3- 12_020+_31951866_sp Cas9	CTCTGCAGGTTGGTGTA ATCAGC	2119	CUCUGCAGGUUGGU GUAUUC	2527	AGC
GuideDesign3_ABE_N GC_20nt_3-9_008_- 31946593_spCas9	GCCCTCAAACCTCTGCA CTCTGC	2120	GCCCUCAAACCUCU GCACUC	2528	TGC
GuideDesign3_ABE_N GC_20nt_3-9_008_- 31947507_spCas9	AAAGGTCACCTTGGCAG GAAGGC	2121	AAAGGUCACCUUGG CAGGAA	2529	GGC
GuideDesign3_ABE_N GC_20nt_3- 9_008+_31947936_spC as9	GCACCCAGGGGAACAAC AGAAGC	2122	GCACCCAGGGGAAC AACAGA	2530	AGC
GuideDesign3_ABE_N GC_20nt_3- 9_008+_31951139_spC as9	CCAGAGGAAGAGCTGCT CCCTGC	2123	CCAGAGGAAGAGCU GCUCCC	2531	TGC
GuideDesign3_ABE_N GC_20nt_3- 9_008+_31951545_spC as9	TCCTTGCAGGTGATTCT GGCGGC	2124	UCCUUGCAGGUGAU UCUGGC	2532	GGC
GuideDesign3_ABE_N GG_20nt_3-12_018_- 31946271_spCas9	CTCGCTTACCTCCAGAC AAGAGG	2125	CUCGCUUACCUCCA GACAAG	2533	AGG
GuideDesign3_ABE_N GG_20nt_3-12_018_- 31947508_spCas9	CAAAGGTCACCTTGGCA GGAAGG	2126	CAAAGGUCACCUUG GCAGGA	2534	AGG
GuideDesign3_ABE_N GG_20nt_3-12_018_- 31948947_spCas9	CCTTCTGACCATCAGTC ATGAGG	2127	CCUUCUGACCAUCA GUCAUG	2535	AGG

Guide polynucleotide name	Target sequence	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
GuideDesign3_ABE_N GG_20nt_3-12_018_- 31949325_spCas9	TCACCCAGATAATCCTC CCTTGG	2128	UCACCCAGAUAAUC CUCCCU	2536	TGG
GuideDesign3_ABE_N GG_20nt_3-12_018_- 31949546_spCas9	GTATCTCCCTACCGATC ATTTGG	2129	GUAUCUCCCUACCG AUCAUU	2537	TGG
GuideDesign3_ABE_N GG_20nt_3-12_018_- 31950130_spCas9	GCTTACAATGACTGAGA TCTTGG	2130	GCUUACAAUGACUG AGAUCU	2538	TGG
GuideDesign3_ABE_N GG_20nt_3-12_018_- 31950760_spCas9	GACGCTCTCACCTGATA GTCTGG	2131	GACGCUCUCACCUG AUAGUC	2539	TGG
GuideDesign3_ABE_N GG_20nt_3-12_018_- 31950926_spCas9	CTTACTTTGTTGCTGGC AAGTGG	2132	CUUACUUUGUUGCU GGCAAG	2540	TGG
GuideDesign3_ABE_N GG_20nt_3-12_018_- 31950933_spCas9	AGTATGTCTTACTTTGT TGCTGG	2133	AGUAUGUCUUACUU UGUUGC	2541	TGG
GuideDesign3_ABE_N GG_20nt_3-12_018_- 31951456_spCas9	TCTCACCTCTGCAAGTA TTGGGG	2134	UCUCACCUCUGCAA GUAUUG	2542	GGG
GuideDesign3_ABE_N GG_20nt_3-12_018_- 31951457_spCas9	CTCTCACCTCTGCAAGT ATTGGG	2135	CUCUCACCUCUGCA AGUAUU	2543	GGG
GuideDesign3_ABE_N GG_20nt_3-12_018_- 31951458_spCas9	TCTCTCACCTCTGCAAG TATTGG	2136	UCUCUCACCUCUGC AAGUAU	2544	TGG
GuideDesign3_ABE_N GG_20nt_3- 12_018_+_31947938_sp Cas9	ACCCAGGGGAACAACAG AAGCGG	2137	ACCCAGGGGAACAA CAGAAG	2545	CGG
GuideDesign3_ABE_N GG_20nt_3- 12_018_+_31948364_sp Cas9	CACCCACAGGTGGCAAG TTATGG	2138	CACCCACAGGUGGC AAGUUA	2546	TGG
GuideDesign3_ABE_N GG_20nt_3- 12_018_+_31948825_sp Cas9	ACAGACCACAAGTTGAA GTCAGG	2139	ACAGACCACAAGUU GAAGUC	2547	AGG
GuideDesign3_ABE_N GG_20nt_3- 12_018_+_31949234_sp Cas9	TTCTGCAGGATTGCACA ACATGG	2140	UUCUGCAGGAUUGC ACAACA	2548	TGG
GuideDesign3_ABE_N GG_20nt_3- 12_018_+_31949235_sp Cas9	TCTGCAGGATTGCACAA CATGGG	2141	UCUGCAGGAUUGCA CAACAU	2549	GGG
GuideDesign3_ABE_N GG_20nt_3- 12_018_+_31949238_sp Cas9	GCAGGATTGCACAACAT GGGCGG	2142	GCAGGAUUGCACAA CAUGGG	2550	CGG

Guide polynucleotide name	Target sequence	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
GuideDesign3_ABE_N GG_20nt_3- 12_018+_31949412_sp Cas9	CCCTCAGATGTCTATGT GTTTGG	2143	CCCUCAGAUGUCUA UGUGUU	2551	TGG
GuideDesign3_ABE_N GG_20nt_3- 12_018+_31949413_sp Cas9	CCTCAGATGTCTATGTG TTTGGG	2144	CCUCAGAUGUCUAU GUGUUU	2552	GGG
GuideDesign3_ABE_N GG_20nt_3- 12_018+_31949414_sp Cas9	CTCAGATGTCTATGTGT TTGGGG	2145	CUCAGAUGUCUAUG UGUUUG	2553	GGG
GuideDesign3_ABE_N GG_20nt_3- 12_018+_31950275_sp Cas9	GTGTCCCCAGCGCCCTT CAAAGG	2146	GUGUCCCCAGCGCC CUUCA	2554	AGG
GuideDesign3_ABE_N GG_20nt_3- 12_018+_31950276_sp Cas9	TGTCCCCAGCGCCCTTC AAAGGG	2147	UGUCCCCAGCGCCC UUCAAA	2555	GGG
GuideDesign3_ABE_N GG_20nt_3- 12_018+_31950609_sp Cas9	CTACTTCAGGAGGGGAG AAGCGG	2148	CUACUUCAGGAGGG GAGAAG	2556	CGG
GuideDesign3_ABE_N GG_20nt_3- 12_018+_31950610_sp Cas9	TACTTCAGGAGGGGAGA AGCGGG	2149	UACUUCAGGAGGGG AGAAGC	2557	GGG
GuideDesign3_ABE_N GG_20nt_3- 12_018+_31951541_sp Cas9	CCTCTCCTTGCAGGTGA TTCTGG	2150	CCUCUCCUUGCAGG UGAUUC	2558	TGG
GuideDesign3_ABE_N GG_20nt_3- 12_018+_31951544_sp Cas9	CTCCTTGCAGGTGATTC TGGCGG	2151	CUCCUUGCAGGUGA UUCUGG	2559	CGG
GuideDesign3_ABE_N GG_20nt_3- 12_018+_31951869_sp Cas9	TGCAGGTTGGTGTAATC AGCTGG	2152	UGCAGGUUGGUGUA AUCAGC	2560	TGG
GuideDesign3_ABE_N GG_20nt_3- 12_018+_31951870_sp Cas9	GCAGGTTGGTGTAATCA GCTGGG	2153	GCAGGUUGGUGUAA UCAGCU	2561	GGG
GuideDesign3_ABE_N GG_20nt_3-9_002_- 31951457_spCas9	CTCTCACCTCTGCAAGT ATTGGG	2154	CUCUCACCUCUGCA AGUAUU	2562	GGG
GuideDesign3_ABE_N GG_20nt_3-9_002_- 31951458_spCas9	TCTCTCACCTCTGCAAG TATTGG	2155	UCUCUCACCUCUGC AAGUAU	2563	TGG

Guide polynucleotide name	Target sequence	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
GuideDesign3_ABE_N GG_20nt_3- 9_002+_31947938_spC as9	ACCCAGGGGAACAACAG AAGCGG	2156	ACCCAGGGGAACAA CAGAAG	2564	CGG
GuideDesign3_ABE_N GG_20nt_3- 9_002+_31949234_spC as9	TTCTGCAGGATTGCACA ACATGG	2157	UUCUGCAGGAUUGC ACAACA	2565	TGG
GuideDesign3_ABE_N NNRRT_21nt_5- 14_014_- 31948945 saCas9	TCCCTTCTGACCATCAG TCATGAGGAT	2158	UCCCUUCUGACCAU CAGUCAU	2566	GAGG AT
GuideDesign3_ABE_N NNRRT_21nt_5- 14_014_- 31949323 saCas9	ACTCACCCAGATAATCC TCCCTTGGGT	2159	ACUCACCCAGAUAA UCCUCCC	2567	TTGG GT
GuideDesign3_ABE_N NNRRT_21nt_5- 14_014_- 31950382 saCas9	CCTTACCTACGCTGACC TTGATTGAGT	2160	CCUUACCUACGCUG ACCUUGA	2568	TTGA GT
GuideDesign3_ABE_N NNRRT_21nt_5- 14_014_- 31951226 saCas9	GTTTCTCACCTTATCCC CATCTTGAT	2161	GUUUCUCACCUUUAU CCCCAUU	2569	CTTG AT
GuideDesign3_ABE_N NNRRT_21nt_5- 14_014_- 31951455 saCas9	TTCTCTCACCTCTGCAA GTATTGGGGT	2162	UUCUCUCACCUCUG CAAGUAU	2570	TGGG GT
GuideDesign3_ABE_N NNRRT_21nt_5- 14_014+_31948361_sa Cas9	CCTCACCCACAGGTGGC AAGTTATGGT	2163	CCUCACCCACAGGU GGCAAGU	2571	TATG GT
GuideDesign3_ABE_N NNRRT_21nt_5- 14_014+_31949411_sa Cas9	TCCCTCAGATGTCTATG TGTTTGGGGT	2164	UCCCUUCAGAUUCU AUGUGUU	2572	TGGG GT
GuideDesign3_ABE_N NNRRT_21nt_5- 14_014+_31950034_sa Cas9	CTCCTTCTCTGCCAGAT GAAAGCCAGT	2165	CUCCUUCUCUGCCA GAUGAAA	2573	GCCA GT
GuideDesign3_ABE_N NNRRT_21nt_5- 14_014+_31950042_sa Cas9	CTGCCAGATGAAAGCCA GTCTCTGAGT	2166	CUGCCAGAUGAAAG CCAGUCU	2574	CTGA GT
GuideDesign3_ABE_VT TN_22nt_5-9_017_- 31946593 cas12b	ATTGCCCTCAAACCTCT GCACTCTGC	2167	CCCUCAAACCUCUG CACUCUGC	2575	ATTG
GuideDesign3_ABE_VT TN_22nt_5-9_017_- 31950134 cas12b	ATTCTGTGCTTACAATG ACTGAGATC	2168	UGUGCUUACAAUGA CUGAGAUC	2576	ATTC

Guide polynucleotide name	Target sequence	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
GuideDesign3_ABE_VT TN_22nt_5-9_017_- 31950390_cas12b	GTTGCATCCTTACCTAC GCTGACCTT	2169	CAUCCUUACCUACG CUGACCUU	2577	GTTG
GuideDesign3_ABE_VT TN_22nt_5-9_017_- 31951457_cas12b	ATTCTCTCACCTCTGCA AGTATTGGG	2170	UCUCACCUCUGCAA GUAUUGGG	2578	ATTC
GuideDesign3_ABE_VT TN_22nt_5- 9_017_+_31946360_cas 12b	CTTCTCTTCAGGTGTG ACCACCACT	2171	CUCUUCAGGUGUGA CCACCACU	2579	CTTT
GuideDesign3_ABE_VT TN_22nt_5- 9_017_+_31946996_cas 12b	CTTCTCAAAGCAATCCA CTGTCCAAG	2172	UCAAAGCAAUCCAC UGUCCAAG	2580	CTTC
GuideDesign3_ABE_VT TN_22nt_5- 9_017_+_31950037_cas 12b	CTTCTCTGCCAGATGAA AGCCAGTCT	2173	UCUGCCAGAUGAAA GCCAGUCU	2581	CTTC
GuideDesign3_ABE_VT TN_22nt_5- 9_017_+_31950272_cas 12b	GTTGTGTCCCCAGCGCC CTTCAAAGG	2174	UGUCCCCAGCGCCC UUCAAAGG	2582	GTTG
GuideDesign3_ABE_VT TN_22nt_5- 9_017_+_31950853_cas 12b	CTTGTCTTTTATAGGCC CATTTGTCT	2175	UCCUUUAUAGGCC AUUUGUCU	2583	CTTG
GuideDesign3_ABE_VT TN_22nt_5- 9_017_+_31951133_cas 12b	ATTCGTCCAGAGGAAGA GCTGCTCCC	2176	GUCCAGAGGAAGAG CUGCUC	2584	ATTC
GuideDesign3_CBE_N NGRRT_21nt_3- 12_012_- 31948945_saCas9	TCCCTTCTGACCATCAG TCATGAGGAT	2177	UCCCUUCUGACCAU CAGUCAU	2585	GAGG AT
GuideDesign3_CBE_N NGRRT_21nt_3- 12_012_- 31949323_saCas9	ACTCACCCAGATAATCC TCCCTTGGGT	2178	ACUCACCCAGAUAA UCCUCCC	2586	TTGG GT
GuideDesign3_CBE_N NGRRT_21nt_3- 12_012_- 31950382_saCas9	CCTTACCTACGCTGACC TTGATTGAGT	2179	CCUUACCUACGCUG ACCUUGA	2587	TTGA GT
GuideDesign3_CBE_N NGRRT_21nt_3- 12_012_- 31951455_saCas9	TTCTCTCACCTCTGCAA GTATTGGGGT	2180	UUCUCUACCUCUG CAAGUAU	2588	TGGG GT
GuideDesign3_CBE_N NNRRT_21nt_3- 12_015_- 31947176_saCas9	ATGCTTCTCACCTCCGT TGTCACAGAT	2181	AUGCUUCUACCUC CGUUGUC	2589	ACAG AT

Guide polynucleotide name	Target sequence	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
GuideDesign3_CBE_N NNRRT_2Int_3- 12_015_- 31947927 saCas9	TGTTGTTCCCTGGGTG CCAGGAGAGT	2182	UGUUGUCCCCUGG GUGCCAG	2590	GAGA GT
GuideDesign3_CBE_N NNRRT_2Int_3- 12_015_- 31948942 saCas9	CTTCTGACCATCAGTCA TGAGGATGAT	2183	CUUCUGACCAUCAG UCAUGAG	2591	GATG AT
GuideDesign3_CBE_N NNRRT_2Int_3- 12_015_- 31948945 saCas9	TCCCTTCTGACCATCAG TCATGAGGAT	2184	UCCCUUCUGACCAU CAGUCAU	2592	GAGG AT
GuideDesign3_CBE_N NNRRT_2Int_3- 12_015_- 31949323 saCas9	ACTCACCCAGATAATCC TCCCTTGGGT	2185	ACUCACCCAGAUAA UCCUCCC	2593	TTGG GT
GuideDesign3_CBE_N NNRRT_2Int_3- 12_015_- 31949397 saCas9	GACATCTGAGGGATAAA AAGGAAGGAT	2186	GACAUCUGAGGGAU AAAAAGG	2594	AAGG AT
GuideDesign3_CBE_N NNRRT_2Int_3- 12_015_- 31950031 saCas9	GGCTTTCATCTGGCAGA GAAGGAGAAAT	2187	GGCUUUCaucUGGC AGAGAAG	2595	GAGA AT
GuideDesign3_CBE_N NNRRT_2Int_3- 12_015_- 31950382 saCas9	CCTTACCTACGCTGACC TTGATTGAGT	2188	CCUUACCUACGCUG ACCUUGA	2596	TTGA GT
GuideDesign3_CBE_N NNRRT_2Int_3- 12_015_- 31950387 saCas9	TGCATCCTTACCTACGC TGACCCTTGAT	2189	UGCAUCCUUACCUA CGCUGAC	2597	CTTG AT
GuideDesign3_CBE_N NNRRT_2Int_3- 12_015_- 31950925 saCas9	TGTCTTACTTTGTTGCT GGCAAGTGGT	2190	UGUCUUACUUUGUU GCUGGCA	2598	AGTG GT
GuideDesign3_CBE_N NNRRT_2Int_3- 12_015_- 31950928 saCas9	GTATGTCTTACTTTGTT GCTGGCAAGT	2191	GUAUGUCUUACUUU GUUGCUG	2599	GCAA GT
GuideDesign3_CBE_N NNRRT_2Int_3- 12_015_- 31951226 saCas9	GTTTCTCACCTTATCCC CATTCTTGAT	2192	GUUUCUCACCUUUA CCCCAUU	2600	CTTG AT
GuideDesign3_CBE_N NNRRT_2Int_3- 12_015_- 31951455 saCas9	TTCTCTCACCTCTGCAA GTATTGGGGT	2193	UUCUCUCACCUCUG CAAGUAU	2601	TGGG GT
GuideDesign3_CBE_N NNRRT_2Int_3-	TACACCAACCTGCAGAG GCAGTGGGGT	2194	UACACCAACCUGCA GAGGCAG	2602	TGGG GT

Guide polynucleotide name	Target sequence	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
12_015 - 31951856 saCas9					
GuideDesign10_CBE_N GA_20nt_4-9_006 - 31946352 spCas9	CACCTGAAGAGAAAGGC TGATGA	2195	CACCUGAAGAGAAA GGCUGA	2603	TGA
GuideDesign10_CBE_N GA_20nt_4-9_006 - 31946990 spCas9	TGGATTGCTTTGAGAAG GGGGGA	2196	UGGAUUGCUUUGAG AAGGGG	2604	GGA
GuideDesign10_CBE_N GA_20nt_4-9_006 - 31947331 spCas9	TACCCCGCTGCAGAGGT ATGAGA	2197	UACCCCGCUGCAGA GGUAUG	2605	AGA
GuideDesign10_CBE_N GA_20nt_4-9_006 - 31947722 spCas9	GAGTCTGGGAGAGTCAG AAATGA	2198	GAGUCUGGGAGAGU CAGAAA	2606	TGA
GuideDesign10_CBE_N GA_20nt_4-9_006 - 31950849 spCas9	TGGGCCTATAAAGGACA AGGAGA	2199	UGGGCCUAUAAAGG ACAAGG	2607	AGA
GuideDesign10_CBE_N GA_20nt_4-9_006 - 31950851 spCas9	AATGGGCCTATAAAGGA CAAGGA	2200	AAUGGGCCUAUAAA GGACAA	2608	GGA
GuideDesign10_CBE_N GA_20nt_4-9_006 - 31951323 spCas9	GCCTTTCTGTAGGGGAG GTGGGA	2201	GCCUUUCUGUAGGG GAGGUG	2609	GGA
GuideDesign10_CBE_N GG_20nt_4-9_003 - 31946991 spCas9	GTGGATTGCTTTGAGAA GGGGGG	2202	GUGGAUUGCUUUGA GAAGGG	2610	GGG
GuideDesign10_CBE_N GG_20nt_4-9_003 - 31949226 spCas9	TGCAATCCTGCAGAAGA GACAGG	2203	UGCAAUCCUGCAGA AGAGAC	2611	AGG
GuideDesign10_CBE_N GG_20nt_4-9_003 - 31949399 spCas9	CATCTGAGGGATAAAAA GGAAGG	2204	CAUCUGAGGGAUAA AAAGGA	2612	AGG
GuideDesign10_CBE_N GG_20nt_4-9_003 - 31949403 spCas9	TAGACATCTGAGGGATA AAAAGG	2205	UAGACAUCUGAGGG AUAAAA	2613	AGG
GuideDesign10_CBE_N GG_20nt_4-9_003 - 31950600 spCas9	CCCTCCTGAAGTAGGAG AGTAGG	2206	CCCUCCUGAAGUAG GAGAGU	2614	AGG
GuideDesign10_CBE_N GG_20nt_4-9_003 - 31950852 spCas9	AAATGGGCCTATAAAGG ACAAGG	2207	AAAUGGGCCUAUAA AGGACA	2615	AGG
GuideDesign10_CBE_N GG_20nt_4-9_003 - 31951324 spCas9	TGCCTTTCTGTAGGGGA GGTGGG	2208	UGCCUUUCUGUAGG GGAGGU	2616	GGG
GuideDesign10_CBE_N GG_20nt_4-9_003 - 31951857 spCas9	ACCAACCTGCAGAGGCA GTGGGG	2209	ACCAACCUGCAGAG GCAGUG	2617	GGG
GuideDesign3_ABE_N GA_20nt_3-9_005 - 31947177 spCas9	CTTCTCACCTCCGTTGT CACAGA	2210	CUUCUCACCUCCGU UGUCAC	2618	AGA

Guide polynucleotide name	Target sequence	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
GuideDesign3_ABE_N GA_20nt_3-9_005_- 31947177_spCas9	CTTCTCACCTCCGTTGT CACAGA	2211	CUUCUCACCUCCGU UGUCAC	2619	AGA
GuideDesign3_ABE_N GA_20nt_3-9_005_- 31948943_spCas9	CTGACCATCAGTCATGA GGATGA	2212	CUGACCAUCAGUCA UGAGGA	2620	TGA
GuideDesign3_ABE_N GA_20nt_3-9_005_- 31948943_spCas9	CTGACCATCAGTCATGA GGATGA	2213	CUGACCAUCAGUCA UGAGGA	2621	TGA
GuideDesign3_ABE_N GA_20nt_3-9_005_- 31949542_spCas9	CTCCCTACCGATCATTT GGTAGA	2214	CUCCCUACCGAUCA UUUGGU	2622	AGA
GuideDesign3_ABE_N GA_20nt_3-9_005_- 31949542_spCas9	CTCCCTACCGATCATTT GGTAGA	2215	CUCCCUACCGAUCA UUUGGU	2623	AGA
GuideDesign3_ABE_N GA_20nt_3-9_005_- 31950384_spCas9	TTACCTACGCTGACCTT GATTGA	2216	UUACCUACGCUGAC CUUGAU	2624	TGA
GuideDesign3_ABE_N GA_20nt_3-9_005_- 31950384_spCas9	TTACCTACGCTGACCTT GATTGA	2217	UUACCUACGCUGAC CUUGAU	2625	TGA
GuideDesign3_ABE_N GA_20nt_3-9_005_- 31950388_spCas9	ATCCTTACCTACGCTGA CCTTGA	2218	AUCCUUACCUACGC UGACCU	2626	TGA
GuideDesign3_ABE_N GA_20nt_3-9_005_- 31950388_spCas9	ATCCTTACCTACGCTGA CCTTGA	2219	AUCCUUACCUACGC UGACCU	2627	TGA
GuideDesign3_ABE_N GA_20nt_3-9_005_- 31951227_spCas9	TCTCACCTTATCCCCAT TCTTGA	2220	UCUCACCUUAUCCC CAUUCU	2628	TGA
GuideDesign3_ABE_N GA_20nt_3-9_005_- 31951227_spCas9	TCTCACCTTATCCCCAT TCTTGA	2221	UCUCACCUUAUCCC CAUUCU	2629	TGA
GuideDesign3_ABE_N GA_20nt_3-9_005_- 31951591_spCas9	GAGGACTCACTTGAATG AAACGA	2222	GAGGACUCACUUGA AUGAAA	2630	CGA
GuideDesign3_ABE_N GA_20nt_3-9_005_- 31951591_spCas9	GAGGACTCACTTGAATG AAACGA	2223	GAGGACUCACUUGA AUGAAA	2631	CGA
GuideDesign3_ABE_N GA_20nt_3- 9_005_+_31947000_spC as9	TCAAAGCAATCCACTGT CCAAGA	2224	UCAAAGCAAUCCAC UGUCCA	2632	AGA
GuideDesign3_ABE_N GA_20nt_3- 9_005_+_31947000_spC as9	TCAAAGCAATCCACTGT CCAAGA	2225	UCAAAGCAAUCCAC UGUCCA	2633	AGA
GuideDesign3_ABE_N GA_20nt_3- 9_005_+_31947734_spC as9	CTCCCAGACTCCTTCAT GTACGA	2226	CUCCCAGACUCCUU CAUGUA	2634	CGA

Guide polynucleotide name	Target sequence	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
GuideDesign3_ABE_NGA_20nt_3-9_005+_31947734_spCas9	CTCCCAGACTCCTTCATGTACGA	2227	CUCCCAGACUCCUUAUGUA	2635	CGA
GuideDesign3_ABE_NGA_20nt_3-9_005+_31947939_spCas9	CCCAGGGGAACAACAGAAGCGGA	2228	CCCAGGGGAACAACAGAAGC	2636	GGA
GuideDesign3_ABE_NGA_20nt_3-9_005+_31947939_spCas9	CCCAGGGGAACAACAGAAGCGGA	2229	CCCAGGGGAACAACAGAAGC	2637	GGA
GuideDesign3_ABE_NGA_20nt_3-9_005+_31948369_spCas9	ACAGGTGGCAAGTTATGTTGTGA	2230	ACAGGUGGCAAGUUAUGGUG	2638	TGA
GuideDesign3_ABE_NGA_20nt_3-9_005+_31948369_spCas9	ACAGGTGGCAAGTTATGTTGTGA	2231	ACAGGUGGCAAGUUAUGGUG	2639	TGA
GuideDesign3_ABE_NGA_20nt_3-9_005+_31950044_spCas9	GCCAGATGAAAGCCAGTCTCTGA	2232	GCCAGAUGAAAGCCAGUCUC	2640	TGA
GuideDesign3_ABE_NGA_20nt_3-9_005+_31950044_spCas9	GCCAGATGAAAGCCAGTCTCTGA	2233	GCCAGAUGAAAGCCAGUCUC	2641	TGA
GuideDesign3_ABE_NGA_20nt_3-9_005+_31950277_spCas9	GTCCCCAGCGCCCTTCA AAGGGA	2234	GUCCCCAGCGCCCUUCAAAG	2642	GGA
GuideDesign3_ABE_NGA_20nt_3-9_005+_31950277_spCas9	GTCCCCAGCGCCCTTCA AAGGGA	2235	GUCCCCAGCGCCCUUCAAAG	2643	GGA
GuideDesign3_ABE_NGA_20nt_3-9_005+_31951335_spCas9	TACAGAAAGGCAGCTGTGAGAGA	2236	UACAGAAAGGCAGCUGUGAG	2644	AGA
GuideDesign3_ABE_NGA_20nt_3-9_005+_31951335_spCas9	TACAGAAAGGCAGCTGTGAGAGA	2237	UACAGAAAGGCAGCUGUGAG	2645	AGA
GuideDesign3_ABE_NGC_20nt_3-9_008_-31946270_spCas9	TCGCTTACCTCCAGACAAGAGGC	2238	UCGCUUACCUCCAGACAAGA	2646	GGC
GuideDesign3_ABE_NGC_20nt_3-9_008_-31946270_spCas9	TCGCTTACCTCCAGACAAGAGGC	2239	UCGCUUACCUCCAGACAAGA	2647	GGC

Guide polynucleotide name	Target sequence	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
GuideDesign3_ABE_N GC_20nt_3-9_008_- 31947173_spCas9	TCACCTCCGTTGTCACA GATCGC	2240	UCACCUCCGUUGUC ACAGAU	2648	CGC
GuideDesign3_ABE_N GC_20nt_3-9_008_- 31947173_spCas9	TCACCTCCGTTGTCACA GATCGC	2241	UCACCUCCGUUGUC ACAGAU	2649	CGC
GuideDesign3_ABE_N GC_20nt_3-9_008_- 31950129_spCas9	CTTACAATGACTGAGAT CTTGGC	2242	CUUACAAUGACUGA GAUCUU	2650	GGC
GuideDesign3_ABE_N GC_20nt_3-9_008_- 31950129_spCas9	CTTACAATGACTGAGAT CTTGGC	2243	CUUACAAUGACUGA GAUCUU	2651	GGC
GuideDesign3_ABE_N GC_20nt_3-9_008_- 31950759_spCas9	ACGCTCTCACCTGATAG TCTGGC	2244	ACGCUCUCACCUGA UAGUCU	2652	GGC
GuideDesign3_ABE_N GC_20nt_3-9_008_- 31950759_spCas9	ACGCTCTCACCTGATAG TCTGGC	2245	ACGCUCUCACCUGA UAGUCU	2653	GGC
GuideDesign3_ABE_N GC_20nt_3- 9_008_+_31949236_spC as9	CTGCAGGATTGCACAAC ATGGGC	2246	CUGCAGGAUUGCAC AACAU	2654	GGC
GuideDesign3_ABE_N GC_20nt_3- 9_008_+_31949236_spC as9	CTGCAGGATTGCACAAC ATGGGC	2247	CUGCAGGAUUGCAC AACAU	2655	GGC
GuideDesign3_ABE_N GC_20nt_3- 9_008_+_31950863_spC as9	ATAGGCCCATTTGTCTC CCCTGC	2248	AUAGGCCCAUUUGU CUCCCC	2656	TGC
GuideDesign3_ABE_N GC_20nt_3- 9_008_+_31950863_spC as9	ATAGGCCCATTTGTCTC CCCTGC	2249	AUAGGCCCAUUUGU CUCCCC	2657	TGC
GuideDesign3_ABE_N GC_20nt_3- 9_008_+_31951866_spC as9	CTCTGCAGGTTGGTGTA ATCAGC	2250	CUCUGCAGGUUGGU GUAAUC	2658	AGC
GuideDesign3_ABE_N GC_20nt_3- 9_008_+_31951866_spC as9	CTCTGCAGGTTGGTGTA ATCAGC	2251	CUCUGCAGGUUGGU GUAAUC	2659	AGC
GuideDesign3_ABE_N GG_20nt_3-9_002_- 31946271_spCas9	CTCGCTTACCTCCAGAC AAGAGG	2252	CUCGCUUACCUCCA GACAAG	2660	AGG
GuideDesign3_ABE_N GG_20nt_3-9_002_- 31946271_spCas9	CTCGCTTACCTCCAGAC AAGAGG	2253	CUCGCUUACCUCCA GACAAG	2661	AGG
GuideDesign3_ABE_N GG_20nt_3-9_002_- 31947508_spCas9	CAAAGGTCACCTTGGCA GGAAGG	2254	CAAAGGUCACCUUG GCAGGA	2662	AGG

Guide polynucleotide name	Target sequence	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
GuideDesign3_ABE_N GG_20nt_3-9_002_- 31947508_spCas9	CAAAGGTCACCTTGGCA GGAAGG	2255	CAAAGGUCACCUUG GCAGGA	2663	AGG
GuideDesign3_ABE_N GG_20nt_3-9_002_- 31948947_spCas9	CCTTCTGACCATCAGTC ATGAGG	2256	CCUUCUGACCAUCA GUCAUG	2664	AGG
GuideDesign3_ABE_N GG_20nt_3-9_002_- 31948947_spCas9	CCTTCTGACCATCAGTC ATGAGG	2257	CCUUCUGACCAUCA GUCAUG	2665	AGG
GuideDesign3_ABE_N GG_20nt_3-9_002_- 31949325_spCas9	TCACCCAGATAATCCTC CCTTGG	2258	UCACCCAGAUAAUC CUCCCU	2666	TGG
GuideDesign3_ABE_N GG_20nt_3-9_002_- 31949325_spCas9	TCACCCAGATAATCCTC CCTTGG	2259	UCACCCAGAUAAUC CUCCCU	2667	TGG
GuideDesign3_ABE_N GG_20nt_3-9_002_- 31950130_spCas9	GCTTACAATGACTGAGA TCTTGG	2260	GCUUACAAUGACUG AGAUCU	2668	TGG
GuideDesign3_ABE_N GG_20nt_3-9_002_- 31950130_spCas9	GCTTACAATGACTGAGA TCTTGG	2261	GCUUACAAUGACUG AGAUCU	2669	TGG
GuideDesign3_ABE_N GG_20nt_3-9_002_- 31950926_spCas9	CTTACTTTGTTGCTGGC AAGTGG	2262	CUUACUUUGUUGCU GGCAAG	2670	TGG
GuideDesign3_ABE_N GG_20nt_3-9_002_- 31950926_spCas9	CTTACTTTGTTGCTGGC AAGTGG	2263	CUUACUUUGUUGCU GGCAAG	2671	TGG
GuideDesign3_ABE_N GG_20nt_3-9_002_- 31951456_spCas9	TCTCACCTCTGCAAGTA TTGGGG	2264	UCUCACCUCUGCAA GUAUUG	2672	GGG
GuideDesign3_ABE_N GG_20nt_3-9_002_- 31951456_spCas9	TCTCACCTCTGCAAGTA TTGGGG	2265	UCUCACCUCUGCAA GUAUUG	2673	GGG
GuideDesign3_ABE_N GG_20nt_3-9_002_+ 31948364_spCas9	CACCCACAGGTGGCAAG TTATGG	2266	CACCCACAGGUGGC AAGUUA	2674	TGG
GuideDesign3_ABE_N GG_20nt_3-9_002_+ 31948364_spCas9	CACCCACAGGTGGCAAG TTATGG	2267	CACCCACAGGUGGC AAGUUA	2675	TGG
GuideDesign3_ABE_N GG_20nt_3-9_002_+ 31948825_spCas9	ACAGACCACAAGTTGAA GTCAGG	2268	ACAGACCACAAGUU GAAGUC	2676	AGG
GuideDesign3_ABE_N GG_20nt_3-9_002_+ 31948825_spCas9	ACAGACCACAAGTTGAA GTCAGG	2269	ACAGACCACAAGUU GAAGUC	2677	AGG
GuideDesign3_ABE_N GG_20nt_3-9_002_+ 31948825_spCas9	TCTGCAGGATTGCACAA CATGGG	2270	UCUGCAGGAUUGCA CAACAU	2678	GGG

Guide polynucleotide name	Target sequence	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
9_002+_31949235_spCas9					
GuideDesign3_ABE_NGG_20nt_3-9_002+_31949235_spCas9	TCTGCAGGATTGCACAACATGGG	2271	UCUGCAGGAUUGCAACAACAU	2679	GGG
GuideDesign3_ABE_NGG_20nt_3-9_002+_31949238_spCas9	GCAGGATTGCACAACATGGGCGG	2272	GCAGGAUUGCACAACAUGGG	2680	CGG
GuideDesign3_ABE_NGG_20nt_3-9_002+_31949238_spCas9	GCAGGATTGCACAACATGGGCGG	2273	GCAGGAUUGCACAACAUGGG	2681	CGG
GuideDesign3_ABE_NGG_20nt_3-9_002+_31949412_spCas9	CCCTCAGATGTCTATGTGTTTGG	2274	CCCUCAGAUGUCUAUGUGUUU	2682	TGG
GuideDesign3_ABE_NGG_20nt_3-9_002+_31949412_spCas9	CCCTCAGATGTCTATGTGTTTGG	2275	CCCUCAGAUGUCUAUGUGUUU	2683	TGG
GuideDesign3_ABE_NGG_20nt_3-9_002+_31949413_spCas9	CCTCAGATGTCTATGTGTTTGGG	2276	CCUCAGAUGUCUAUGUGUUU	2684	GGG
GuideDesign3_ABE_NGG_20nt_3-9_002+_31949413_spCas9	CCTCAGATGTCTATGTGTTTGGG	2277	CCUCAGAUGUCUAUGUGUUU	2685	GGG
GuideDesign3_ABE_NGG_20nt_3-9_002+_31949414_spCas9	CTCAGATGTCTATGTGTTTGGGG	2278	CUCAGAUGUCUAUGUGUUUG	2686	GGG
GuideDesign3_ABE_NGG_20nt_3-9_002+_31949414_spCas9	CTCAGATGTCTATGTGTTTGGGG	2279	CUCAGAUGUCUAUGUGUUUG	2687	GGG
GuideDesign3_ABE_NGG_20nt_3-9_002+_31950275_spCas9	GTGTCCCCAGCGCCCTTCAAAGG	2280	GUGUCCCCAGCGCCCUUCA	2688	AGG
GuideDesign3_ABE_NGG_20nt_3-9_002+_31950275_spCas9	GTGTCCCCAGCGCCCTTCAAAGG	2281	GUGUCCCCAGCGCCCUUCA	2689	AGG
GuideDesign3_ABE_NGG_20nt_3-9_002+_31950276_spCas9	TGTCCCCAGCGCCCTTCAAAGGG	2282	UGUCCCCAGCGCCCUUCAA	2690	GGG

Guide polynucleotide name	Target sequence	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
GuideDesign3_ABE_N GG_20nt_3- 9_002+_31950276_spC as9	TGTCCCCAGCGCCCTTC AAAGGG	2283	UGUCCCCAGCGCCC UUCAAA	2691	GGG
GuideDesign3_ABE_N GG_20nt_3- 9_002+_31950609_spC as9	CTACTTCAGGAGGGGAG AAGCGG	2284	CUACUUCAGGAGGG GAGAAG	2692	CGG
GuideDesign3_ABE_N GG_20nt_3- 9_002+_31950609_spC as9	CTACTTCAGGAGGGGAG AAGCGG	2285	CUACUUCAGGAGGG GAGAAG	2693	CGG
GuideDesign3_ABE_N GG_20nt_3- 9_002+_31950610_spC as9	TACTTCAGGAGGGGAGA AGCGGG	2286	UACUUCAGGAGGGG AGAAGC	2694	GGG
GuideDesign3_ABE_N GG_20nt_3- 9_002+_31950610_spC as9	TACTTCAGGAGGGGAGA AGCGGG	2287	UACUUCAGGAGGGG AGAAGC	2695	GGG
GuideDesign3_ABE_N GG_20nt_3- 9_002+_31951544_spC as9	CTCCTTGCAGGTGATTC TGGCGG	2288	CUCCUUGCAGGUGA UUCUGG	2696	CGG
GuideDesign3_ABE_N GG_20nt_3- 9_002+_31951544_spC as9	CTCCTTGCAGGTGATTC TGGCGG	2289	CUCCUUGCAGGUGA UUCUGG	2697	CGG
GuideDesign3_ABE_N GG_20nt_3- 9_002+_31951869_spC as9	TGCAGGTTGGTGTAATC AGCTGG	2290	UGCAGGUUGGUGUA AUCAGC	2698	TGG
GuideDesign3_ABE_N GG_20nt_3- 9_002+_31951869_spC as9	TGCAGGTTGGTGTAATC AGCTGG	2291	UGCAGGUUGGUGUA AUCAGC	2699	TGG
GuideDesign3_ABE_N GG_20nt_3- 9_002+_31951870_spC as9	GCAGGTTGGTGTAATCA GCTGGG	2292	GCAGGUUGGUGUAA UCAGCU	2700	GGG
GuideDesign3_ABE_N GG_20nt_3- 9_002+_31951870_spC as9	GCAGGTTGGTGTAATCA GCTGGG	2293	GCAGGUUGGUGUAA UCAGCU	2701	GGG
GuideDesign3_ABE_N NGRRT_21nt_5- 14_011_- 31948945 saCas9	TCCCTTCTGACCATCAG TCATGAGGAT	2294	UCCCUUCUGACCAU CAGUCAU	2702	GAGG AT
GuideDesign3_ABE_N NGRRT_21nt_5-	TCCCTTCTGACCATCAG TCATGAGGAT	2295	UCCCUUCUGACCAU CAGUCAU	2703	GAGG AT

Guide polynucleotide name	Target sequence	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
14_011_- 31948945 saCas9					
GuideDesign3_ABE_N NGRRT_21nt_5- 14_011_- 31949323 saCas9	ACTCACCCAGATAATCC TCCCTTGGGT	2296	ACUCACCCAGAUAA UCCUCCC	2704	TTGG GT
GuideDesign3_ABE_N NGRRT_21nt_5- 14_011_- 31949323 saCas9	ACTCACCCAGATAATCC TCCCTTGGGT	2297	ACUCACCCAGAUAA UCCUCCC	2705	TTGG GT
GuideDesign3_ABE_N NGRRT_21nt_5- 14_011_- 31950382 saCas9	CCTTACCTACGCTGACC TTGATTGAGT	2298	CCUUACCUACGCUG ACCUUGA	2706	TTGA GT
GuideDesign3_ABE_N NGRRT_21nt_5- 14_011_- 31950382 saCas9	CCTTACCTACGCTGACC TTGATTGAGT	2299	CCUUACCUACGCUG ACCUUGA	2707	TTGA GT
GuideDesign3_ABE_N NGRRT_21nt_5- 14_011_- 31951455 saCas9	TTCTCTCACCTCTGCAA GTATTGGGGT	2300	UUCUCUCACCUCUG CAAGUAA	2708	TGGG GT
GuideDesign3_ABE_N NGRRT_21nt_5- 14_011_- 31951455 saCas9	TTCTCTCACCTCTGCAA GTATTGGGGT	2301	UUCUCUCACCUCUG CAAGUAA	2709	TGGG GT
GuideDesign3_ABE_N NGRRT_21nt_5- 14_011_+_31949411_sa Cas9	TCCCTCAGATGTCTATG TGTTTGGGGT	2302	UCCCUCAGAUGUCU AUGUGUU	2710	TGGG GT
GuideDesign3_ABE_N NGRRT_21nt_5- 14_011_+_31949411_sa Cas9	TCCCTCAGATGTCTATG TGTTTGGGGT	2303	UCCCUCAGAUGUCU AUGUGUU	2711	TGGG GT
GuideDesign3_ABE_N NGRRT_21nt_5- 14_011_+_31950042_sa Cas9	CTGCCAGATGAAAGCCA GTCTCTGAGT	2304	CUGCCAGAUGAAAG CCAGUCU	2712	CTGA GT
GuideDesign3_ABE_N NGRRT_21nt_5- 14_011_+_31950042_sa Cas9	CTGCCAGATGAAAGCCA GTCTCTGAGT	2305	CUGCCAGAUGAAAG CCAGUCU	2713	CTGA GT
GuideDesign3_ABE_N NNRRT_21nt_5- 14_014_- 31947176 saCas9	ATGCTTCTCACCTCCGT TGTCACAGAT	2306	AUGCUUCUCACCUC CGUUGUC	2714	ACAG AT
GuideDesign3_ABE_N NNRRT_21nt_5- 14_014_- 31947176 saCas9	ATGCTTCTCACCTCCGT TGTCACAGAT	2307	AUGCUUCUCACCUC CGUUGUC	2715	ACAG AT

Guide polynucleotide name	Target sequence	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
GuideDesign3_ABE_N NNRRT_21nt_5- 14_014_- 31948067 saCas9	AGGAGGATTCCACCTTC TCAATTAAGT	2308	AGGAGGAUCCACC UUCUCAA	2716	TTAAGT
GuideDesign3_ABE_N NNRRT_21nt_5- 14_014_- 31948067 saCas9	AGGAGGATTCCACCTTC TCAATTAAGT	2309	AGGAGGAUCCACC UUCUCAA	2717	TTAAGT
GuideDesign3_ABE_N NNRRT_21nt_5- 14_014_- 31948499 saCas9	CCCTAACCTCTGACCTT CATAATTGAT	2310	CCCUAACCUCUGAC CUUCAUA	2718	ATTGAT
GuideDesign3_ABE_N NNRRT_21nt_5- 14_014_- 31948499 saCas9	CCCTAACCTCTGACCTT CATAATTGAT	2311	CCCUAACCUCUGAC CUUCAUA	2719	ATTGAT
GuideDesign3_ABE_N NNRRT_21nt_5- 14_014_- 31948942 saCas9	CTTCTGACCATCAGTCA TGAGGATGAT	2312	CUUCUGACCAUCAG UCAUGAG	2720	GATGAT
GuideDesign3_ABE_N NNRRT_21nt_5- 14_014_- 31948942 saCas9	CTTCTGACCATCAGTCA TGAGGATGAT	2313	CUUCUGACCAUCAG UCAUGAG	2721	GATGAT
GuideDesign3_ABE_N NNRRT_21nt_5- 14_014_- 31949545 saCas9	CTTGTATCTCCCTACCG ATCATTTGGT	2314	CUUGUAUCUCCCUA CCGAUCA	2722	TTTGTG
GuideDesign3_ABE_N NNRRT_21nt_5- 14_014_- 31949545 saCas9	CTTGTATCTCCCTACCG ATCATTTGGT	2315	CUUGUAUCUCCCUA CCGAUCA	2723	TTTGTG
GuideDesign3_ABE_N NNRRT_21nt_5- 14_014_- 31950135 saCas9	GGATTCTGTGCTTACAA TGACTGAGAT	2316	GGAUUCUGUGCUUA CAAUGAC	2724	TGAGAT
GuideDesign3_ABE_N NNRRT_21nt_5- 14_014_- 31950135 saCas9	GGATTCTGTGCTTACAA TGACTGAGAT	2317	GGAUUCUGUGCUUA CAAUGAC	2725	TGAGAT
GuideDesign3_ABE_N NNRRT_21nt_5- 14_014_- 31950387 saCas9	TGCATCCTTACCTACGC TGACCTTGAT	2318	UGCAUCCUUACCUA CGCUGAC	2726	CTTGAT
GuideDesign3_ABE_N NNRRT_21nt_5- 14_014_- 31950387 saCas9	TGCATCCTTACCTACGC TGACCTTGAT	2319	UGCAUCCUUACCUA CGCUGAC	2727	CTTGAT
GuideDesign3_ABE_N NNRRT_21nt_5-	TGTCTTACTTTGTTGCT GGCAAGTGGT	2320	UGUCUUACUUUGUU GCUGGCA	2728	AGTGTG

Guide polynucleotide name	Target sequence	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
14_014_- 31950925_saCas9					
GuideDesign3_ABE_N NNRRT_2Int_5- 14_014_- 31950925_saCas9	TGTCTTACTTTGTTGCT GGCAAGTGGT	2321	UGUCUUACUUUGUU GCUGGCA	2729	AGTG GT
GuideDesign3_ABE_N NNRRT_2Int_5- 14_014_- 31950928_saCas9	GTATGTCTTACTTTGTT GCTGGCAAGT	2322	GUAUGUCUUACUUU GUUGCUG	2730	GCAA GT
GuideDesign3_ABE_N NNRRT_2Int_5- 14_014_- 31950928_saCas9	GTATGTCTTACTTTGTT GCTGGCAAGT	2323	GUAUGUCUUACUUU GUUGCUG	2731	GCAA GT
GuideDesign3_ABE_N NNRRT_2Int_5- 14_014_+_31946366_sa Cas9	CTTCAGGTGTGACCACC ACTCCATGGT	2324	CUUCAGGUGUGACC ACCACUC	2732	CATG GT
GuideDesign3_ABE_N NNRRT_2Int_5- 14_014_+_31946366_sa Cas9	CTTCAGGTGTGACCACC ACTCCATGGT	2325	CUUCAGGUGUGACC ACCACUC	2733	CATG GT
GuideDesign3_ABE_N NNRRT_2Int_5- 14_014_+_31948817_sa Cas9	CCCTCTCCACAGACCAC AAGTTGAAGT	2326	CCCUCUCCACAGAC CACAAGU	2734	TGAA GT
GuideDesign3_ABE_N NNRRT_2Int_5- 14_014_+_31948817_sa Cas9	CCCTCTCCACAGACCAC AAGTTGAAGT	2327	CCCUCUCCACAGAC CACAAGU	2735	TGAA GT
GuideDesign3_ABE_N NNRRT_2Int_5- 14_014_+_31951334_sa Cas9	CTACAGAAAGGCAGCTG TGAGAGAGAT	2328	CUACAGAAAGGCAG CUGUGAG	2736	AGAG AT
GuideDesign3_ABE_N NNRRT_2Int_5- 14_014_+_31951334_sa Cas9	CTACAGAAAGGCAGCTG TGAGAGAGAT	2329	CUACAGAAAGGCAG CUGUGAG	2737	AGAG AT
GuideDesign3_CBE_N NGRRT_2Int_3- 12_012_- 31947927_saCas9	TGTTGTTCCCTGGGTG CCAGGAGAGT	2330	UGUUGUCCCCUGG GUGCCAG	2738	GAGA GT
GuideDesign3_CBE_N NGRRT_2Int_3- 12_012_- 31947927_saCas9	TGTTGTTCCCTGGGTG CCAGGAGAGT	2331	UGUUGUCCCCUGG GUGCCAG	2739	GAGA GT
GuideDesign3_CBE_N NGRRT_2Int_3- 12_012_- 31949397_saCas9	GACATCTGAGGGATAAA AAGGAAGGAT	2332	GACAUCUGAGGGAU AAAAAGG	2740	AAGG AT

Guide polynucleotide name	Target sequence	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
GuideDesign3_CBE_N NGRRT_21nt_3- 12_012_- 31949397 saCas9	GACATCTGAGGGATAAA AAGGAAGGAT	2333	GACAUCUGAGGGAU AAAAAGG	2741	AAGG AT
GuideDesign3_CBE_N NGRRT_21nt_3- 12_012_- 31950031 saCas9	GGCTTTCATCTGGCAGA GAAGGAGAAAT	2334	GGCUUUCAUCUGGC AGAGAAG	2742	GAGA AT
GuideDesign3_CBE_N NGRRT_21nt_3- 12_012_- 31950031 saCas9	GGCTTTCATCTGGCAGA GAAGGAGAAAT	2335	GGCUUUCAUCUGGC AGAGAAG	2743	GAGA AT
GuideDesign3_CBE_N NGRRT_21nt_3- 12_012_- 31951856 saCas9	TACACCAACCTGCAGAG GCAGTGGGGT	2336	UACACCAACCUGCA GAGGCAG	2744	TGGG GT
GuideDesign3_CBE_N NGRRT_21nt_3- 12_012_- 31951856 saCas9	TACACCAACCTGCAGAG GCAGTGGGGT	2337	UACACCAACCUGCA GAGGCAG	2745	TGGG GT
GuideDesign3_CBE_N NNRRT_21nt_3- 12_015_- 31946263 saCas9	CTTACCTCCAGACAAGA GGCCCAAGAT	2338	CUUACCUCAGACA AGAGGCC	2746	CAAG AT
GuideDesign3_CBE_N NNRRT_21nt_3- 12_015_- 31946263 saCas9	CTTACCTCCAGACAAGA GGCCCAAGAT	2339	CUUACCUCAGACA AGAGGCC	2747	CAAG AT
GuideDesign3_CBE_N NNRRT_21nt_3- 12_015_- 31946354 saCas9	TGGTCACACCTGAAGAG AAAGGCTGAT	2340	UGGUCACACCUGAA GAGAAAG	2748	GCTG AT
GuideDesign3_CBE_N NNRRT_21nt_3- 12_015_- 31946354 saCas9	TGGTCACACCTGAAGAG AAAGGCTGAT	2341	UGGUCACACCUGAA GAGAAAG	2749	GCTG AT
GuideDesign3_CBE_N NNRRT_21nt_3- 12_015_- 31946985 saCas9	GGATTGCTTTGAGAAGG GGGGACAAGT	2342	GGAUUGC UUUGAGA AGGGGGG	2750	ACAA GT
GuideDesign3_CBE_N NNRRT_21nt_3- 12_015_- 31946985 saCas9	GGATTGCTTTGAGAAGG GGGGACAAGT	2343	GGAUUGC UUUGAGA AGGGGGG	2751	ACAA GT
GuideDesign3_CBE_N NNRRT_21nt_3- 12_015_- 31947322 saCas9	CGCTGCAGAGGTATGAG ACATCGAGGT	2344	CGCUGCAGAGGU AU GAGACAU	2752	CGAG GT
GuideDesign3_CBE_N NNRRT_21nt_3-	CGCTGCAGAGGTATGAG ACATCGAGGT	2345	CGCUGCAGAGGU AU GAGACAU	2753	CGAG GT

Guide polynucleotide name	Target sequence	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
12_015 - 31947322 saCas9					
GuideDesign3_CBE_N NNRRT_21nt_3- 12_015 - 31947719 saCas9	GGAGTCTGGGAGAGTCA GAAATGAGGT	2346	GGAGUCUGGGAGAG UCAGAAA	2754	TGAG GT
GuideDesign3_CBE_N NNRRT_21nt_3- 12_015 - 31947719 saCas9	GGAGTCTGGGAGAGTCA GAAATGAGGT	2347	GGAGUCUGGGAGAG UCAGAAA	2755	TGAG GT
GuideDesign3_CBE_N NNRRT_21nt_3- 12_015 - 31947724 saCas9	ATGAAGGAGTCTGGGAG AGTCAGAAAT	2348	AUGAAGGAGUCUGG GAGAGUC	2756	AGAA AT
GuideDesign3_CBE_N NNRRT_21nt_3- 12_015 - 31947724 saCas9	ATGAAGGAGTCTGGGAG AGTCAGAAAT	2349	AUGAAGGAGUCUGG GAGAGUC	2757	AGAA AT
GuideDesign3_CBE_N NNRRT_21nt_3- 12_015 - 31950269 saCas9	TTTGAAGGGCGCTGGGG ACACAACAGT	2350	UUUGAAGGGCGCUG GGGACAC	2758	AACA GT
GuideDesign3_CBE_N NNRRT_21nt_3- 12_015 - 31950269 saCas9	TTTGAAGGGCGCTGGGG ACACAACAGT	2351	UUUGAAGGGCGCUG GGGACAC	2759	AACA GT
GuideDesign3_CBE_N NNRRT_21nt_3- 12_015 - 31950599 saCas9	CTCCCCCTCCTGAAGTAG GAGAGTAGGT	2352	CUCCCCUCCUGAAG UAGGAGA	2760	GTAG GT
GuideDesign3_CBE_N NNRRT_21nt_3- 12_015 - 31950599 saCas9	CTCCCCCTCCTGAAGTAG GAGAGTAGGT	2353	CUCCCCUCCUGAAG UAGGAGA	2761	GTAG GT
GuideDesign3_CBE_N NNRRT_21nt_3- 12_015 - 31950922 saCas9	CTTACTTTGTTGCTGGC AAGTGGTAGT	2354	CUUACUUUGUUGCU GGCAAGU	2762	GGTA GT
GuideDesign3_CBE_N NNRRT_21nt_3- 12_015 - 31950922 saCas9	CTTACTTTGTTGCTGGC AAGTGGTAGT	2355	CUUACUUUGUUGCU GGCAAGU	2763	GGTA GT
GuideDesign10_CBE_N GC_20nt_4-9_009 - 31947141 spCas9	ACTCCATCGGCCATTCA CTTGGC	2356	ACUCCAUCGGCCAU UCACUU	2764	GGC
GuideDesign10_CBE_N GC_20nt_4-9_009 - 31948418 spCas9	ACCCAAATTTTGGGGTA TGTGGC	2357	ACCCAAAUUUUGGG GUAUGU	2765	GGC
GuideDesign10_CBE_N GC_20nt_4-9_009 - 31948461 spCas9	CGTGACCCAGTCTGCAT TACTGC	2358	CGUGACCCAGUCUG CAUUAAC	2766	TGC

Guide polynucleotide name	Target sequence	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
GuideDesign10_CBE_NGC_20nt_4-9_009+_31946572_spCas9	GACCAAAAGACTGTCAGGAAGGC	2359	GACCAAAAGACUGUCAGGAA	2767	GGC
GuideDesign10_CBE_NGC_20nt_4-9_009+_31947152_spCas9	GGCCGATGGAGTGGGCA GACAGC	2360	GGCCGAUGGAGUGG GCAGAC	2768	AGC
GuideDesign10_CBE_NGC_20nt_4-9_009+_31947758_spCas9	ACCCCTCAAGAGGTGGC CGAAGC	2361	ACCCCUCAAGAGGU GGCCGA	2769	AGC
GuideDesign10_CBE_NGC_20nt_4-9_009+_31948862_spCas9	AGGCCCTCCAGGCAGTG TACAGC	2362	AGGCCCUCCAGGCA GUGUAC	2770	AGC
GuideDesign10_CBE_NGC_20nt_4-9_009+_31950757_spCas9	TGGCCAGACTATCAGGT GAGAGC	2363	UGGCCAGACUAUCA GGUGAG	2771	AGC
GuideDesign10_CBE_NGC_20nt_4-9_009+_31950937_spCas9	CAACAAAGTAAGACATA CTGGGC	2364	CAACAAAGUAAGAC AUACUU	2772	GGC
GuideDesign10_CBE_NGC_20nt_4-9_009+_31951925_spCas9	CAAAAGCAGGTACCTGC TCACGC	2365	CAAAAGCAGGUACC UGCUCA	2773	CGC
GuideDesign10_CBE_NGC_20nt_4-9_009+_31951966_spCas9	CCTCTTTCAAGTGCTGC CCTGGC	2366	CCUCUUUCAAGUGC UGCCCCU	2774	GGC
GuideDesign3_CBE_NNGRRT_21nt_3-12_012+_31951994_saCas9	GAGAAACTCCAAGATGA GGATTTGGGT	2367	GAGAAACUCCAAGA UGAGGAU	2775	TTGG GT
GuideDesign3_CBE_NNGRRT_21nt_3-12_015 - 31950102_saCas9	CTGCCATGGTTGCTTGT GGTAATCGGT	2368	CUGCCAUGGUUGCU UGUGGUA	2776	ATCG GT
GuideDesign3_CBE_NNGRRT_21nt_3-12_015+_31946459_saCas9	TTCTCCAAGAGGGCCAG GCACTGGAGT	2369	UUCUCCAAGAGGGC CAGGCAC	2777	TGGA GT
GuideDesign3_CBE_NNGRRT_21nt_3-12_015+_31946513_saCas9	ACCCTGTGCAGACACGT ACCTGCAGAT	2370	ACCCUGUGCAGACA CGUACCU	2778	GCAG AT
GuideDesign3_CBE_NNGRRT_21nt_3-	ACCAAAAGACTGTCAGG AAGGCAGAGT	2371	ACCAAAAGACUGUC AGGAAGG	2779	CAGA GT

Guide polynucleotide name	Target sequence	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
12_015+_31946573_sa Cas9					
GuideDesign3_CBE_N NNRRT_21nt_3- 12_015+_31947137_sa Cas9	ACCTGCCAAGTGAATGG CCGATGGAGT	2372	ACCUGCCAAGUGAA UGGCCGA	2780	TGGA GT
GuideDesign3_CBE_N NNRRT_21nt_3- 12_015+_31949486_sa Cas9	AGACAATGAGCAACATG TGTTCAAAAGT	2373	AGACAAUGAGCAAC AUGUGUU	2781	CAAA GT
GuideDesign3_CBE_N NNRRT_21nt_3- 12_015+_31949493_sa Cas9	GAGCAACATGTGTTCAA AGTCAAGGAT	2374	GAGCAACAUGUGUU CAAAGUC	2782	AAGG AT
GuideDesign3_CBE_N NNRRT_21nt_3- 12_015+_31950110_sa Cas9	CCACAAGCAACCATGGC AGGCCAAGAT	2375	CCACAAGCAACCAU GGCAGGC	2783	CAAG AT
GuideDesign3_CBE_N NNRRT_21nt_3- 12_015+_31951909_sa Cas9	CAAAAACCAGAAGCGGC AAAAGCAGGT	2376	CAAAAACCAGAAGC GGCAAAA	2784	GCAG GT
GuideDesign3_CBE_N NNRRT_21nt_3- 12_015+_31951994_sa Cas9	GAGAAACTCCAAGATGA GGATTTGGGT	2377	GAGAAACUCCAAGA UGAGGAU	2785	TTGG GT
GuideDesign10_CBE_N GA_20nt_4-9_006_- 31946539_spCas9	AGGGTGCTCCAGGACCC CGTAGA	2378	AGGGUGCUCCAGGA CCCCGU	2786	AGA
GuideDesign10_CBE_N GA_20nt_4-9_006_- 31947033_spCas9	GGGCCAGTATTCCCCGT TCTCGA	2379	GGGCCAGUAUUCCC CGUUCU	2787	CGA
GuideDesign10_CBE_N GA_20nt_4-9_006_- 31947477_spCas9	CGCTCCAAGAGCCACCT TCCTGA	2380	CGCUCCAAGAGCCA CCUUC	2788	TGA
GuideDesign10_CBE_N GA_20nt_4-9_006_- 31948907_spCas9	GCGGTTCCAGCCTTCAG GAGGGA	2381	GCGGUUCCAGCCUU CAGGAG	2789	GGA
GuideDesign10_CBE_N GA_20nt_4-9_006_- 31950068_spCas9	GTTCCCAAACCATGCCA CAGAGA	2382	GUUCCCAAACCAUG CCACAG	2790	AGA
GuideDesign10_CBE_N GA_20nt_4-9_006_- 31950070_spCas9	GTGTTCCCAAACCATGC CACAGA	2383	GUGUCCCAAACCA UGCCAC	2791	AGA
GuideDesign10_CBE_N GA_20nt_4-9_006_- 31951968_spCas9	CAGCCAGGGCAGCACTT GAAAGA	2384	CAGCCAGGGCAGCA CUUGAA	2792	AGA
GuideDesign10_CBE_N GA_20nt_4-9_006_- 31951972_spCas9	CCTTCAGCCAGGGCAGC ACTTGA	2385	CCUUCAGCCAGGGC AGCACU	2793	TGA

Guide polynucleotide name	Target sequence	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
GuideDesign10_CBE_NGA_20nt_4-9_006+_31946404_spCas9	CCCCAGGGATCCTGCTCTCTGGA	2386	CCCCAGGGAUCCUGCUCUCU	2794	GGA
GuideDesign10_CBE_NGA_20nt_4-9_006+_31946568_spCas9	TCAAGACCAAAAGACTGTCAGGA	2387	UCAAGACCAAAAGACUGUCA	2795	GGA
GuideDesign10_CBE_NGA_20nt_4-9_006+_31947135_spCas9	GCACCTGCCAAGTGAATGGCCGA	2388	GCACCUGCCAAGUGAAUGGC	2796	CGA
GuideDesign10_CBE_NGA_20nt_4-9_006+_31947139_spCas9	CTGCCAAGTGAATGGCCGATGGA	2389	CUGCCAAGUGAAUGGCCGAU	2797	GGA
GuideDesign10_CBE_NGA_20nt_4-9_006+_31947148_spCas9	GAATGGCCGATGGAGTGGCAGA	2390	GAAUGGCCGAUGGAGUGGGC	2798	AGA
GuideDesign10_CBE_NGA_20nt_4-9_006+_31947161_spCas9	AGTGGGCAGACAGCGATCTGTGA	2391	AGUGGGCAGACAGCGAUCUG	2799	TGA
GuideDesign10_CBE_NGA_20nt_4-9_006+_31947394_spCas9	GGCAGCCAGTACCGCCTTGAAGA	2392	GGCAGCCAGUACCGCCUUGA	2800	AGA
GuideDesign10_CBE_NGA_20nt_4-9_006+_31947460_spCas9	TCCCAGCGGCGAACGTGTCAGGA	2393	UCCCAGCGGCGAACGUGUCA	2801	GGA
GuideDesign10_CBE_NGA_20nt_4-9_006+_31947474_spCas9	GTGTCAGGAAGGTGGCTCTTGGA	2394	GUGUCAGGAAGGUGGCUCUU	2802	GGA
GuideDesign10_CBE_NGA_20nt_4-9_006+_31947942_spCas9	AGGGGAACAACAGAAAGCGAAGA	2395	AGGGGAACAACAGAGCGGA	2803	AGA
GuideDesign10_CBE_NGA_20nt_4-9_006+_31948866_spCas9	CCTCCAGGCAGTGTACAGCATGA	2396	CCUCCAGGCAGUGUACAGCA	2804	TGA
GuideDesign10_CBE_NGA_20nt_4-9_006+_31949541_spCas9	TTCTACCAAATGATCGGTAGGGA	2397	UUCUACCAAUAUGAUCGGUAG	2805	GGA
GuideDesign10_CBE_NGA_20nt_4-	CTACCAAATGATCGGTAGGAGA	2398	CUACCAAUAUGAUCGGUAGGG	2806	AGA

Guide polynucleotide name	Target sequence	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
9_006_+_31949543_spCas9					
GuideDesign10_CBE_NGA_20nt_4-9_006_+_31950113_spCas9	CAAGCAACCATGGCAGGCCAAGA	2399	CAAGCAACCAUGGCAGGCCA	2807	AGA
GuideDesign10_CBE_NGA_20nt_4-9_006_+_31950755_spCas9	TATGGCCAGACTATCAGGTGAGA	2400	UAUGGCCAGACUAUCAGGUG	2808	AGA
GuideDesign10_CBE_NGA_20nt_4-9_006_+_31950927_spCas9	CAC TTGCCAGCAACAAA GTAAGA	2401	CACUUGCCAGCAACAAAGUA	2809	AGA
GuideDesign10_CBE_NGA_20nt_4-9_006_+_31951361_spCas9	GCTCAATATGCCCCAGGCTATGA	2402	GCUCAUAUAGCCCCAGGCUA	2810	TGA
GuideDesign10_CBE_NGA_20nt_4-9_006_+_31951969_spCas9	CTTTC AAGTGCTGCCCTGGCTGA	2403	CUUUCAAGUGCUGCCUGGC	2811	TGA
GuideDesign10_CBE_NGG_20nt_4-9_003_-31947142_spCas9	CACTCCATCGGCCATTCACTTGG	2404	CACUCCAUCGGCCA UUCACU	2812	TGG
GuideDesign10_CBE_NGG_20nt_4-9_003_-31948419_spCas9	GACCCAAATTTTGGGGTATGTGG	2405	GACCCAAAUUUUGGGUAUG	2813	TGG
GuideDesign10_CBE_NGG_20nt_4-9_003_-31948908_spCas9	TGCGGTTCCAGCCTTCA GGAGGG	2406	UGCGGUUCCAGCCU UCAGGA	2814	GGG
GuideDesign10_CBE_NGG_20nt_4-9_003_-31948909_spCas9	GTGCGGTTCCAGCCTTCAGGAGG	2407	GUGCGGUUCCAGCCUUCAGG	2815	AGG
GuideDesign10_CBE_NGG_20nt_4-9_003_-31950110_spCas9	TGGCCTGCCATGGTTGCTTGTGG	2408	UGGCCUGCCAUGGU UGCUUG	2816	TGG
GuideDesign10_CBE_NGG_20nt_4-9_003_+_31946448_spCas9	CTCCTTCCGACTTCTCCAAGAGG	2409	CUCCUCCGACUUCUCCAAG	2817	AGG
GuideDesign10_CBE_NGG_20nt_4-9_003_+_31946449_spCas9	TCCTTCCGACTTCTCCAAGAGGG	2410	UCCUCCGACUUCUCCAAGA	2818	GGG
GuideDesign10_CBE_NGG_20nt_4-9_003_+_31946460_spCas9	TCTCCAAGAGGGCCAGGCACTGG	2411	UCUCCAAGAGGGCCAGGCAC	2819	TGG
GuideDesign10_CBE_NGG_20nt_4-	CTCAAGACCAAAAGACTGTCAGG	2412	CUCAAGACCAAAAGACUGUC	2820	AGG

Guide polynucleotide name	Target sequence	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
9_003_+_31946567_spCas9					
GuideDesign10_CBE_NGG_20nt_4-9_003_+_31946571_spCas9	AGACCAAAAGACTGTCA GGAAGG	2413	AGACCAAAAGACUG UCAGGA	2821	AGG
GuideDesign10_CBE_NGG_20nt_4-9_003_+_31947138_spCas9	CCTGCCAAGTGAATGGC CGATGG	2414	CCUGCCAAGUGAAU GGCCGA	2822	TGG
GuideDesign10_CBE_NGG_20nt_4-9_003_+_31947459_spCas9	CTCCAGCGGCGAACGT GTCAGG	2415	CUCCAGCGGCGAA CGUGUC	2823	AGG
GuideDesign10_CBE_NGG_20nt_4-9_003_+_31947463_spCas9	CAGCGGCGAACGTGTCA GGAAGG	2416	CAGCGGCGAACGUG UCAGGA	2824	AGG
GuideDesign10_CBE_NGG_20nt_4-9_003_+_31947466_spCas9	CGGCGAACGTGTCAGGA AGGTGG	2417	CGGCGAACGUGUCA GGAAGG	2825	TGG
GuideDesign10_CBE_NGG_20nt_4-9_003_+_31947473_spCas9	CGTGTCAAGGAAGGTGGC TCTTGG	2418	CGUGUCAGGAAGGU GGCUCU	2826	TGG
GuideDesign10_CBE_NGG_20nt_4-9_003_+_31949539_spCas9	TTTTCTACCAAATGATC GGTAGG	2419	UUUUCUACCAAUG AUCGGU	2827	AGG
GuideDesign10_CBE_NGG_20nt_4-9_003_+_31949540_spCas9	TTTTCTACCAAATGATCG GTAGGG	2420	UUUCUACCAAUGA UCGGUA	2828	GGG
GuideDesign10_CBE_NGG_20nt_4-9_003_+_31950936_spCas9	GCAACAAAGTAAGACAT ACTTGG	2421	GCAACAAAGUAAGA CAUACU	2829	TGG
GuideDesign10_CBE_NGG_20nt_4-9_003_+_31951965_spCas9	ACCTCTTTCAAGTGCTG CCCTGG	2422	ACCUCUUUCAAGUG CUGCCC	2830	TGG
GuideDesign10_CBE_NGG_20nt_4-9_003_+_31951996_spCas9	GAAACTCCAAGATGAGG ATTTGG	2423	GAAACUCCAAGAUG AGGAUU	2831	TGG
GuideDesign10_CBE_NGG_20nt_4-9_003_+_31951997_spCas9	AAACTCCAAGATGAGGA TTTGGG	2424	AAACUCCAAGAUGA GGAUUU	2832	GGG

Guide polynucleotide name	Target sequence	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
GuideDesign3_CBE_N NGRRT_21nt_3- 12_012+_31946459_sa Cas9	TTCTCCAAGAGGGCCAG GCACTGGAGT	2425	UUCUCCAAGAGGGC CAGGCAC	2833	TGGA GT
GuideDesign3_CBE_N NGRRT_21nt_3- 12_012+_31946459_sa Cas9	TTCTCCAAGAGGGCCAG GCACTGGAGT	2426	UUCUCCAAGAGGGC CAGGCAC	2834	TGGA GT
GuideDesign3_CBE_N NGRRT_21nt_3- 12_012+_31946573_sa Cas9	ACCAAAAGACTGTCAGG AAGGCAGAGT	2427	ACCAAAAGACUGUC AGGAAGG	2835	CAGA GT
GuideDesign3_CBE_N NGRRT_21nt_3- 12_012+_31946573_sa Cas9	ACCAAAAGACTGTCAGG AAGGCAGAGT	2428	ACCAAAAGACUGUC AGGAAGG	2836	CAGA GT
GuideDesign3_CBE_N NGRRT_21nt_3- 12_012+_31947137_sa Cas9	ACCTGCCAAGTGAATGG CCGATGGAGT	2429	ACCUGCCAAGUGAA UGGCCGA	2837	TGGA GT
GuideDesign3_CBE_N NGRRT_21nt_3- 12_012+_31947137_sa Cas9	ACCTGCCAAGTGAATGG CCGATGGAGT	2430	ACCUGCCAAGUGAA UGGCCGA	2838	TGGA GT
GuideDesign3_CBE_N NGRRT_21nt_3- 12_012+_31949493_sa Cas9	GAGCAACATGTGTTCAA AGTCAAGGAT	2431	GAGCAACAUGUGUU CAAAGUC	2839	AAGG AT
GuideDesign3_CBE_N NGRRT_21nt_3- 12_012+_31949493_sa Cas9	GAGCAACATGTGTTCAA AGTCAAGGAT	2432	GAGCAACAUGUGUU CAAAGUC	2840	AAGG AT
GuideDesign3_CBE_N NNRRT_21nt_3- 12_015_- 31946530 saCas9	GCTCCAGGACCCCGTAG ATCTGCAGGT	2433	GCUCCAGGACCCCG UAGAUCU	2841	GCAG GT
GuideDesign3_CBE_N NNRRT_21nt_3- 12_015_- 31946530 saCas9	GCTCCAGGACCCCGTAG ATCTGCAGGT	2434	GCUCCAGGACCCCG UAGAUCU	2842	GCAG GT
GuideDesign3_CBE_N NNRRT_21nt_3- 12_015_- 31946538 saCas9	TTCAGGGTGCTCCAGGA CCCCGTAGAT	2435	UUCAGGGUGCUCCA GGACCCC	2843	GTAG AT
GuideDesign3_CBE_N NNRRT_21nt_3- 12_015_- 31946538 saCas9	TTCAGGGTGCTCCAGGA CCCCGTAGAT	2436	UUCAGGGUGCUCCA GGACCCC	2844	GTAG AT
GuideDesign3_CBE_N NNRRT_21nt_3-	GGGGCCAGTATTCCCCG TTCTCGAAGT	2437	GGGGCCAGUAUUC CCGUUCU	2845	CGAA GT

Guide polynucleotide name	Target sequence	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
12_015_- 31947030_saCas9					
GuideDesign3_CBE_N NNRRT_21nt_3- 12_015_- 31947030_saCas9	GGGGCCAGTATTCCCCG TTCTCGAAGT	2438	GGGGCCAGUAUUC CCGUUCU	2846	CGAA GT
GuideDesign3_CBE_N NNRRT_21nt_3- 12_015_- 31947137_saCas9	ACTCCATCGGCCATTCA CTTGGCAGGT	2439	ACUCCAUCGGCCAU UCACUUG	2847	GCAG GT
GuideDesign3_CBE_N NNRRT_21nt_3- 12_015_- 31947137_saCas9	ACTCCATCGGCCATTCA CTTGGCAGGT	2440	ACUCCAUCGGCCAU UCACUUG	2848	GCAG GT
GuideDesign3_CBE_N NNRRT_21nt_3- 12_015_- 31950106_saCas9	TGGCCTGCCATGGTTGC TTGTGGTAAT	2441	UGGCCUGCCAUGGU UGCUGU	2849	GGTA AT
GuideDesign3_CBE_N NNRRT_21nt_3- 12_015_- 31950106_saCas9	TGGCCTGCCATGGTTGC TTGTGGTAAT	2442	UGGCCUGCCAUGGU UGCUGU	2850	GGTA AT
GuideDesign3_CBE_N NNRRT_21nt_3- 12_015_- 31950109_saCas9	TCTTGGCCTGCCATGGT TGCTTGTGGT	2443	UCUUGGCCUGCCAU GGUUGCU	2851	TGTG GT
GuideDesign3_CBE_N NNRRT_21nt_3- 12_015_- 31950109_saCas9	TCTTGGCCTGCCATGGT TGCTTGTGGT	2444	UCUUGGCCUGCCAU GGUUGCU	2852	TGTG GT
GuideDesign3_CBE_N NNRRT_21nt_3- 12_015_- 31951965_saCas9	TCAGCCAGGGCAGCACT TGAAAGAGGT	2445	UCAGCCAGGGCAGC ACUUGAA	2853	AGAG GT
GuideDesign3_CBE_N NNRRT_21nt_3- 12_015_- 31951965_saCas9	TCAGCCAGGGCAGCACT TGAAAGAGGT	2446	UCAGCCAGGGCAGC ACUUGAA	2854	AGAG GT
GuideDesign3_CBE_N NNRRT_21nt_3- 12_015_+_31947132_sa Cas9	ATCGCACCTGCCAAGTG AATGGCCGAT	2447	AUCGCACCUGCCAA GUGAAUG	2855	GCCG AT
GuideDesign3_CBE_N NNRRT_21nt_3- 12_015_+_31947132_sa Cas9	ATCGCACCTGCCAAGTG AATGGCCGAT	2448	AUCGCACCUGCCAA GUGAAUG	2856	GCCG AT
GuideDesign3_CBE_N NNRRT_21nt_3- 12_015_+_31947151_sa Cas9	TGGCCGATGGAGTGGGC AGACAGCGAT	2449	UGGCCGAUGGAGUG GGCAGAC	2857	AGCG AT

Guide polynucleotide name	Target sequence	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
GuideDesign3_CBE_N NNRRT_2Int_3- 12_015+_31947151_sa Cas9	TGGCCGATGGAGTGGGC AGACAGCGAT	2450	UGGCCGAUGGAGUG GGCAGAC	2858	AGCG AT
GuideDesign3_CBE_N NNRRT_2Int_3- 12_015+_31947460_sa Cas9	TCCCAGCGGCGAACGTG TCAGGAAGGT	2451	UCCCAGCGGCGAAC GUGUCAG	2859	GAAG GT
GuideDesign3_CBE_N NNRRT_2Int_3- 12_015+_31947460_sa Cas9	TCCCAGCGGCGAACGTG TCAGGAAGGT	2452	UCCCAGCGGCGAAC GUGUCAG	2860	GAAG GT
GuideDesign3_CBE_N NNRRT_2Int_3- 12_015+_31947939_sa Cas9	CCCAGGGGAACAACAGA AGCGGAAGAT	2453	CCCAGGGGAACAAC AGAAGCG	2861	GAAG AT
GuideDesign3_CBE_N NNRRT_2Int_3- 12_015+_31947939_sa Cas9	CCCAGGGGAACAACAGA AGCGGAAGAT	2454	CCCAGGGGAACAAC AGAAGCG	2862	GAAG AT
GuideDesign3_CBE_N NNRRT_2Int_3- 12_015+_31948478_sa Cas9	GTCACGAAGCAGCTCAA TGAAATCAAT	2455	GUCACGAAGCAGCU CAAUGAA	2863	ATCA AT
GuideDesign3_CBE_N NNRRT_2Int_3- 12_015+_31948478_sa Cas9	GTCACGAAGCAGCTCAA TGAAATCAAT	2456	GUCACGAAGCAGCU CAAUGAA	2864	ATCA AT
GuideDesign3_CBE_N NNRRT_2Int_3- 12_015+_31948863_sa Cas9	GGCCCTCCAGGCAGTGT ACAGCATGAT	2457	GGCCCUCCAGGCAG UGUACAG	2865	CATG AT
GuideDesign3_CBE_N NNRRT_2Int_3- 12_015+_31948863_sa Cas9	GGCCCTCCAGGCAGTGT ACAGCATGAT	2458	GGCCCUCCAGGCAG UGUACAG	2866	CATG AT
GuideDesign3_CBE_N NNRRT_2Int_3- 12_015+_31949540_sa Cas9	TTTCTACCAAATGATCG GTAGGGAGAT	2459	UUUCUACCAAUAUGA UCGGUAG	2867	GGAG AT
GuideDesign3_CBE_N NNRRT_2Int_3- 12_015+_31949540_sa Cas9	TTTCTACCAAATGATCG GTAGGGAGAT	2460	UUUCUACCAAUAUGA UCGGUAG	2868	GGAG AT
GuideDesign3_CBE_N NNRRT_2Int_3- 12_015+_31950116_sa Cas9	GCAACCATGGCAGGCCA AGATCTCAGT	2461	GCAACCAUGGCAGG CCAAGAU	2869	CTCA GT
GuideDesign3_CBE_N NNRRT_2Int_3-	GCAACCATGGCAGGCCA AGATCTCAGT	2462	GCAACCAUGGCAGG CCAAGAU	2870	CTCA GT

Guide polynucleotide name	Target sequence	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
12_015_+_31950116_sa Cas9					

Table 2D. Representative spacer and target site sequences relating to altering a TATA box or start codon of a complement factor B polynucleotide using base editing.

Guide polynucleotide name	Target site description	Editor	Cas description	Target Site	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
GuideDesign90_ABE_NGA_20nt_3-12_019_+_31946067_spCas9	TATA box	ABE_NGA_20nt_3-12_019	spCas9 VRQR IBE	AAAAGGC TGGGGGC TGGTGGG GA	2871	AAAAGGCU GGGGGCUG GUGG	3177	GGA
GuideDesign90_CBE_NGA_20nt_4-9_006_+_31946067_spCas9	TATA box	CBE_NGA_20nt_4-9_006	spCas9 VRQR CBE	AAAAGGC TGGGGGC TGGTGGG GA	2872	AAAAGGCU GGGGGCUG GUGG	3178	GGA
GuideDesign90_CBE_NGA_20nt_3-16_035_+_31946067_spCas9	TATA box	CBE_NGA_20nt_3-16_035	spCas9 IBE extended CBE	AAAAGGC TGGGGGC TGGTGGG GA	2873	AAAAGGCU GGGGGCUG GUGG	3179	GGA
GuideDesign90_ABE_NG_20nt_3-9_027_+_31946067_spCas9	TATA box	ABE_NG_20nt_3-9_027	spCas9 NG ABE	AAAAGGC TGGGGGC TGGTGGG G	2874	AAAAGGCU GGGGGCUG GUGG	3180	GG
GuideDesign90_CBE_NG_20nt_4-9_028_+_31946067_spCas9	TATA box	CBE_NG_20nt_4-9_028	spCas9 NG CBE	AAAAGGC TGGGGGC TGGTGGG G	2875	AAAAGGCU GGGGGCUG GUGG	3181	GG
GuideDesign90_ABE_NRN_20nt_3-9_021_+_31946067_spCas9	TATA box	ABE_NRN_20nt_3-9_021	spCas9 NRN ABE	AAAAGGC TGGGGGC TGGTGGG GA	2876	AAAAGGCU GGGGGCUG GUGG	3182	GGA
GuideDesign90_CBE_NRN_20nt_3-9_022_+_31946067_spCas9	TATA box	CBE_NRN_20nt_3-9_022	spCas9 NRN CBE	AAAAGGC TGGGGGC TGGTGGG GA	2877	AAAAGGCU GGGGGCUG GUGG	3183	GGA
GuideDesign90_MBE_NRN_20nt_3-	TATA box	MBE_NRN_20nt_3-9_023	spCas9 NRN MBE	AAAAGGC TGGGGGC TGGTGGG GA	2878	AAAAGGCU GGGGGCUG GUGG	3184	GGA

Guide polynucleotide name	Target site description	Editor	Cas description	Target Site	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
9_023_+_31946067_spCas9								
GuideDesign90_ABE_NRN_20nt_3-9_021_+_31946068_spCas9	TATA box	ABE_NRN_20nt_3-9_021	spCas9NRNABE	AAAGGCTGGGGGCTGGTGGGGAG	2879	AAAGGCUGGGGGCUGGUGGG	3185	GAG
GuideDesign90_CBE_NRN_20nt_3-9_022_+_31946068_spCas9	TATA box	CBE_NRN_20nt_3-9_022	spCas9NRNCBE	AAAGGCTGGGGGCTGGTGGGGAG	2880	AAAGGCUGGGGGCUGGUGGG	3186	GAG
GuideDesign90_MBE_NRN_20nt_3-9_023_+_31946068_spCas9	TATA box	MBE_NRN_20nt_3-9_023	spCas9NRNMBE	AAAGGCTGGGGGCTGGTGGGGAG	2881	AAAGGCUGGGGGCUGGUGGG	3187	GAG
GuideDesign90_CBE_NRRH_20nt_3-9_031_+_31946068_spCas9	TATA box	CBE_NRRH_20nt_3-9_031	spCas9NRRHCBE	AAAGGCTGGGGGCTGGTGGGGAGC	2882	AAAGGCUGGGGGCUGGUGGG	3188	GAGC
GuideDesign90_ABE_NGC_20nt_3-9_008_+_31946069_spCas9	TATA box	ABE_NGC_20nt_3-9_008	spCas9NGCABE	AAGGCTGGGGGCTGTGGGGAGC	2883	AAGGCUGGGGGCUGGU GGGG	3189	AGC
GuideDesign90_ABE_NGC_20nt_3-12_020_+_31946069_spCas9	TATA box	ABE_NGC_20nt_3-12_020	spCas9NGCIBE	AAGGCTGGGGGCTGTGGGGAGC	2884	AAGGCUGGGGGCUGGU GGGG	3190	AGC
GuideDesign90_CBE_NGC_20nt_4-9_009_+_31946069_spCas9	TATA box	CBE_NGC_20nt_4-9_009	spCas9NGCCBE	AAGGCTGGGGGCTGTGGGGAGC	2885	AAGGCUGGGGGCUGGU GGGG	3191	AGC
GuideDesign90_ABE_NG_20nt_3-9_027_+_31946069_spCas9	TATA box	ABE_NG_20nt_3-9_027	spCas9NGABE	AAGGCTGGGGGCTGTGGGGAG	2886	AAGGCUGGGGGCUGGU GGGG	3192	AG
GuideDesign90_CBE_NG_20nt_4-9_028_+_31946069_spCas9	TATA box	CBE_NG_20nt_4-9_028	spCas9NGCBE	AAGGCTGGGGGCTGTGGGGAG	2887	AAGGCUGGGGGCUGGU GGGG	3193	AG
GuideDesign90_ABE_NRN_20nt_3-9_021	TATA box	ABE_NRN_20nt_3-9_021	spCas9NRNABE	AAGGCTGGGGGCTG	2888	AAGGCUGGGGGCUGGU GGGG	3194	AGC

Guide polynucleotide name	Target site description	Editor	Cas description	Target Site	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
9_021_+_31946069_spCas9				GTGGGGAGC				
GuideDesign90_CBE_NRN_20nt_3-9_022_+_31946069_spCas9	TATA box	CBE_NRN_20nt_3-9_022	spCas9 NRN CBE	AAGGCTG GGGGCTG GTGGGGAGC	2889	AAGGCUGG GGGCUGGU GGGG	3195	AGC
GuideDesign90_MBE_NRN_20nt_3-9_023_+_31946069_spCas9	TATA box	MBE_NRN_20nt_3-9_023	spCas9 NRN MBE	AAGGCTG GGGGCTG GTGGGGAGC	2890	AAGGCUGG GGGCUGGU GGGG	3196	AGC
GuideDesign90_ABE_NRCH_20nt_3-9_024_+_31946069_spCas9	TATA box	ABE_NRCH_20nt_3-9_024	spCas9 NRCH ABE	AAGGCTG GGGGCTG GTGGGGAGCA	2891	AAGGCUGG GGGCUGGU GGGG	3197	AGCA
GuideDesign90_CBE_NRCH_20nt_3-9_030_+_31946069_spCas9	TATA box	CBE_NRCH_20nt_3-9_030	spCas9 NRCH CBE	AAGGCTG GGGGCTG GTGGGGAGCA	2892	AAGGCUGG GGGCUGGU GGGG	3198	AGCA
GuideDesign90_ABE_NGG_20nt_3-12_018_-_31946040_spCas9	TATA box	ABE_NGG_20nt_3-12_018	spCas9 IBE	AATCTGT GTTCTGG CACCTGCGG	2893	AAUCUGUG UUCUGGCA CCUG	3199	CGG
GuideDesign90_CBE_NGG_20nt_4-9_003_-_31946040_spCas9	TATA box	CBE_NGG_20nt_4-9_003	spCas9 CBE	AATCTGT GTTCTGG CACCTGCGG	2894	AAUCUGUG UUCUGGCA CCUG	3200	CGG
GuideDesign90_CBE_NGG_20nt_3-9_029_-_31946040_spCas9	TATA box	CBE_NGG_20nt_3-9_029	spCas9 NGG CBE	AATCTGT GTTCTGG CACCTGCGG	2895	AAUCUGUG UUCUGGCA CCUG	3201	CGG
GuideDesign90_CBE_NGG_20nt_3-16_033_-_31946040_SpCas9	TATA box	CBE_NGG_20nt_3-16_033	SpCas9 IBE CBE	AATCTGT GTTCTGG CACCTGCGG	2896	AAUCUGUG UUCUGGCA CCUG	3202	CGG
GuideDesign90_ABE_NG_20nt_3-9_027_-_	TATA box	ABE_NG_20nt_3-9_027	spCas9 NG ABE	AATCTGT GTTCTGG CACCTGCG	2897	AAUCUGUG UUCUGGCA CCUG	3203	CG

Guide polynucleotide name	Target site description	Editor	Cas description	Target Site	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
_31946041_sp Cas9								
GuideDesign90_CBE_NG_20nt_4-9_028_- _31946041_sp Cas9	TATA box	CBE_NG_20nt_4-9_028	spCas9 NG CBE	AATCTGT GTTCTGG CACCTGC G	2898	AAUCUGUG UUCUGGCA CCUG	3204	CG
GuideDesign90_ABE_NRN_20nt_3-9_021_- _31946040_sp Cas9	TATA box	ABE_NRN_20nt_3-9_021	spCas9 NRN ABE	AATCTGT GTTCTGG CACCTGC GG	2899	AAUCUGUG UUCUGGCA CCUG	3205	CGG
GuideDesign90_CBE_NRN_20nt_3-9_022_- _31946040_sp Cas9	TATA box	CBE_NRN_20nt_3-9_022	spCas9 NRN CBE	AATCTGT GTTCTGG CACCTGC GG	2900	AAUCUGUG UUCUGGCA CCUG	3206	CGG
GuideDesign90_MBE_NRN_20nt_3-9_023_- _31946040_sp Cas9	TATA box	MBE_NRN_20nt_3-9_023	spCas9 NRN MBE	AATCTGT GTTCTGG CACCTGC GG	2901	AAUCUGUG UUCUGGCA CCUG	3207	CGG
GuideDesign90_CBE_NRRH_20nt_3-9_031_- _31946039_sp Cas9	TATA box	CBE_NRRH_20nt_3-9_031	spCas9 NRRH CBE	AATCTGT GTTCTGG CACCTGC GGC	2902	AAUCUGUG UUCUGGCA CCUG	3208	CGGC
GuideDesign90_ABE_NGC_20nt_3-9_008_- _31946042_sp Cas9	TATA box	ABE_NGC_20nt_3-9_008	spCas9 NGC ABE	ACAATCT GTGTTCT GGCACCT GC	2903	ACAAUCUG UGUUCUGG CACC	3209	TGC
GuideDesign90_ABE_NGC_20nt_3-12_020_- _31946042_sp Cas9	TATA box	ABE_NGC_20nt_3-12_020	spCas9 NGC IBE	ACAATCT GTGTTCT GGCACCT GC	2904	ACAAUCUG UGUUCUGG CACC	3210	TGC
GuideDesign90_CBE_NGC_20nt_4-9_009_- _31946042_sp Cas9	TATA box	CBE_NGC_20nt_4-9_009	spCas9 NGC CBE	ACAATCT GTGTTCT GGCACCT GC	2905	ACAAUCUG UGUUCUGG CACC	3211	TGC

Guide polynucleotide name	Target site description	Editor	Cas description	Target Site	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
GuideDesign90_ABE_NG_20nt_3-9_027_-31946043_spCas9	TATA box	ABE_NG_20nt_3-9_027	spCas9 NG ABE	ACAATCTGTGTTCTGGCACCTG	2906	ACAAUCUGUGUUCUGGCACC	3212	TG
GuideDesign90_CBE_NG_20nt_4-9_028_-31946043_spCas9	TATA box	CBE_NG_20nt_4-9_028	spCas9 NG CBE	ACAATCTGTGTTCTGGCACCTG	2907	ACAAUCUGUGUUCUGGCACC	3213	TG
GuideDesign90_ABE_NRN_20nt_3-9_021_-31946042_spCas9	TATA box	ABE_NRN_20nt_3-9_021	spCas9 NRN ABE	ACAATCTGTGTTCTGGCACCTGC	2908	ACAAUCUGUGUUCUGGCACC	3214	TGC
GuideDesign90_CBE_NRN_20nt_3-9_022_-31946042_spCas9	TATA box	CBE_NRN_20nt_3-9_022	spCas9 NRN CBE	ACAATCTGTGTTCTGGCACCTGC	2909	ACAAUCUGUGUUCUGGCACC	3215	TGC
GuideDesign90_MBE_NRN_20nt_3-9_023_-31946042_spCas9	TATA box	MBE_NRN_20nt_3-9_023	spCas9 NRN MBE	ACAATCTGTGTTCTGGCACCTGC	2910	ACAAUCUGUGUUCUGGCACC	3216	TGC
GuideDesign90_ABE_NGG_20nt_3-12_018_+31946054_spCas9	TATA box	ABE_NGG_20nt_3-12_018	spCas9 IBE	ACACAGATTGTATAAAAGGCTGG	2911	ACACAGAUUGUAUAAAAGGC	3217	TGG
GuideDesign90_ABE_NGG_20nt_13-16_032_+31946054_SpCas9	TATA box	ABE_NGG_20nt_13-16_032	SpCas9 IBE_expanded ABE	ACACAGATTGTATAAAAGGCTGG	2912	ACACAGAUUGUAUAAAAGGC	3218	TGG
GuideDesign90_CBE_NGG_20nt_4-9_003_+31946054_spCas9	TATA box	CBE_NGG_20nt_4-9_003	spCas9 CBE	ACACAGATTGTATAAAAGGCTGG	2913	ACACAGAUUGUAUAAAAGGC	3219	TGG
GuideDesign90_CBE_NGG_20nt_3-9_029_+31946054_spCas9	TATA box	CBE_NGG_20nt_3-9_029	spCas9 NGG CBE	ACACAGATTGTATAAAAGGCTGG	2914	ACACAGAUUGUAUAAAAGGC	3220	TGG

Guide polynucleotide name	Target site description	Editor	Cas description	Target Site	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
GuideDesign90_CBE_NGG_20nt_3-16_033_+31946054_SpCas9	TATA box	CBE_NGG_20nt_3-16_033	SpCas9 IBE CBE	ACACAGA TTGTATA AAAGGCT GG	2915	ACACAGAU UGUUAAAA AGGC	3221	TGG
GuideDesign90_ABE_NG_20nt_3-9_027_+31946054_spCas9	TATA box	ABE_NG_20nt_3-9_027	spCas9 NG ABE	ACACAGA TTGTATA AAAGGCT G	2916	ACACAGAU UGUUAAAA AGGC	3222	TG
GuideDesign90_CBE_NG_20nt_4-9_028_+31946054_spCas9	TATA box	CBE_NG_20nt_4-9_028	spCas9 NG CBE	ACACAGA TTGTATA AAAGGCT G	2917	ACACAGAU UGUUAAAA AGGC	3223	TG
GuideDesign90_ABE_NRN_20nt_3-9_021_+31946054_spCas9	TATA box	ABE_NRN_20nt_3-9_021	spCas9 NRN ABE	ACACAGA TTGTATA AAAGGCT GG	2918	ACACAGAU UGUUAAAA AGGC	3224	TGG
GuideDesign90_CBE_NRN_20nt_3-9_022_+31946054_spCas9	TATA box	CBE_NRN_20nt_3-9_022	spCas9 NRN CBE	ACACAGA TTGTATA AAAGGCT GG	2919	ACACAGAU UGUUAAAA AGGC	3225	TGG
GuideDesign90_MBE_NRN_20nt_3-9_023_+31946054_spCas9	TATA box	MBE_NRN_20nt_3-9_023	spCas9 NRN MBE	ACACAGA TTGTATA AAAGGCT GG	2920	ACACAGAU UGUUAAAA AGGC	3226	TGG
GuideDesign90_ABE_NGG_20nt_3-12_018_+31946056_spCas9	TATA box	ABE_NG_20nt_3-12_018	spCas9 IBE	ACAGATT GTATAAA AGGCTGG GG	2921	ACAGAUUG UAUAAAAG GCUG	3227	GGG
GuideDesign90_ABE_NGG_20nt_13-16_032_+31946056_SpCas9	TATA box	ABE_NG_20nt_13-16_032	SpCas9 IBE_expanded ABE	ACAGATT GTATAAA AGGCTGG GG	2922	ACAGAUUG UAUAAAAG GCUG	3228	GGG
GuideDesign90_CBE_NGG_20nt_4-9_003_+31946056_spCas9	TATA box	CBE_NGG_20nt_4-9_003	spCas9 CBE	ACAGATT GTATAAA AGGCTGG GG	2923	ACAGAUUG UAUAAAAG GCUG	3229	GGG
GuideDesign90_CBE_NGG_20nt_3-9_029_+31946056_spCas9	TATA box	CBE_NGG_20nt_3-9_029	spCas9 NGG CBE	ACAGATT GTATAAA AGGCTGG GG	2924	ACAGAUUG UAUAAAAG GCUG	3230	GGG

Guide polynucleotide name	Target site description	Editor	Cas description	Target Site	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
GuideDesign90_CBE_NGG_20nt_3-16_033+_31946056_SpCas9	TATA box	CBE_NGG_20nt_3-16_033	SpCas9 IBE CBE	ACAGATT GTATAAA AGGCTGG GG	2925	ACAGAUUG UAUAAAAG GCUG	3231	GGG
GuideDesign90_ABE_NG_20nt_3-9_027+_31946056_spCas9	TATA box	ABE_NG_20nt_3-9_027	spCas9 NG ABE	ACAGATT GTATAAA AGGCTGG G	2926	ACAGAUUG UAUAAAAG GCUG	3232	GG
GuideDesign90_CBE_NG_20nt_4-9_028+_31946056_spCas9	TATA box	CBE_NG_20nt_4-9_028	spCas9 NG CBE	ACAGATT GTATAAA AGGCTGG G	2927	ACAGAUUG UAUAAAAG GCUG	3233	GG
GuideDesign90_ABE_NRN_20nt_3-9_021+_31946056_spCas9	TATA box	ABE_NRN_20nt_3-9_021	spCas9 NRN ABE	ACAGATT GTATAAA AGGCTGG GG	2928	ACAGAUUG UAUAAAAG GCUG	3234	GGG
GuideDesign90_CBE_NRN_20nt_3-9_022+_31946056_spCas9	TATA box	CBE_NRN_20nt_3-9_022	spCas9 NRN CBE	ACAGATT GTATAAA AGGCTGG GG	2929	ACAGAUUG UAUAAAAG GCUG	3235	GGG
GuideDesign90_MBE_NRN_20nt_3-9_023+_31946056_spCas9	TATA box	MBE_NRN_20nt_3-9_023	spCas9 NRN MBE	ACAGATT GTATAAA AGGCTGG GG	2930	ACAGAUUG UAUAAAAG GCUG	3236	GGG
GuideDesign90_ABE_NGC_20nt_3-12_020+_31946051_spCas9	TATA box	ABE_NGC_20nt_3-12_020	spCas9 NGC IBE	AGAACAC AGATTGT ATAAAAG GC	2931	AGAACACA GAUUGUAU AAAA	3237	GGC
GuideDesign90_CBE_NGC_20nt_4-9_009+_31946051_spCas9	TATA box	CBE_NGC_20nt_4-9_009	spCas9 NGC CBE	AGAACAC AGATTGT ATAAAAG GC	2932	AGAACACA GAUUGUAU AAAA	3238	GGC
GuideDesign90_ABE_NG_20nt_3-9_027+_31946051_spCas9	TATA box	ABE_NG_20nt_3-9_027	spCas9 NG ABE	AGAACAC AGATTGT ATAAAAG G	2933	AGAACACA GAUUGUAU AAAA	3239	GG
GuideDesign90_CBE_NG_20nt_4-9_028+_31946051_spCas9	TATA box	CBE_NG_20nt_4-9_028	spCas9 NG CBE	AGAACAC AGATTGT ATAAAAG G	2934	AGAACACA GAUUGUAU AAAA	3240	GG

Guide polynucleotide name	Target site description	Editor	Cas description	Target Site	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
GuideDesign90_ABE_NRN_20nt_3-9_021+_31946051_spCas9	TATA box	ABE_NRN_20nt_3-9_021	spCas9 NRN ABE	AGAACACAGATTGTATAAAAGGC	2935	AGAACACAGAUGUGUAUAAAA	3241	GGC
GuideDesign90_CBE_NRN_20nt_3-9_022+_31946051_spCas9	TATA box	CBE_NRN_20nt_3-9_022	spCas9 NRN CBE	AGAACACAGATTGTATAAAAGGC	2936	AGAACACAGAUGUGUAUAAAA	3242	GGC
GuideDesign90_MBE_NRN_20nt_3-9_023+_31946051_spCas9	TATA box	MBE_NRN_20nt_3-9_023	spCas9 NRN MBE	AGAACACAGATTGTATAAAAGGC	2937	AGAACACAGAUGUGUAUAAAA	3243	GGC
GuideDesign90_ABE_NRCH_20nt_3-9_024+_31946051_spCas9	TATA box	ABE_NRCH_20nt_3-9_024	spCas9 NRCH ABE	AGAACACAGATTGTATAAAAGGCT	2938	AGAACACAGAUGUGUAUAAAA	3244	GGCT
GuideDesign90_CBE_NRCH_20nt_3-9_030+_31946051_spCas9	TATA box	CBE_NRCH_20nt_3-9_030	spCas9 NRCH CBE	AGAACACAGATTGTATAAAAGGCT	2939	AGAACACAGAUGUGUAUAAAA	3245	GGCT
GuideDesign90_ABE_NGC_20nt_3-9_008+_31946058_spCas9	TATA box	ABE_NGC_20nt_3-9_008	spCas9 NGC ABE	AGATTGTATAAAAGGCTGGGGGC	2940	AGAUUGUAUAAAAGGCUGGG	3246	GGC
GuideDesign90_ABE_NGC_20nt_3-12_020+_31946058_spCas9	TATA box	ABE_NGC_20nt_3-12_020	spCas9 NGC IBE	AGATTGTATAAAAGGCTGGGGGC	2941	AGAUUGUAUAAAAGGCUGGG	3247	GGC
GuideDesign90_CBE_NGC_20nt_4-9_009+_31946058_spCas9	TATA box	CBE_NGC_20nt_4-9_009	spCas9 NGC CBE	AGATTGTATAAAAGGCTGGGGGC	2942	AGAUUGUAUAAAAGGCUGGG	3248	GGC
GuideDesign90_ABE_NG_20nt_3-9_027+_31946058_spCas9	TATA box	ABE_NG_20nt_3-9_027	spCas9 NG ABE	AGATTGTATAAAAGGCTGGGGG	2943	AGAUUGUAUAAAAGGCUGGG	3249	GG
GuideDesign90_CBE_NG_20nt_4-9_028+_31946058_spCas9	TATA box	CBE_NG_20nt_4-9_028	spCas9 NG CBE	AGATTGTATAAAAGGCTGGGGG	2944	AGAUUGUAUAAAAGGCUGGG	3250	GG

Guide polynucleotide name	Target site description	Editor	Cas description	Target Site	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
GuideDesign90_ABE_NRN_20nt_3-9_021+_31946058_spCas9	TATA box	ABE_NRN_20nt_3-9_021	spCas9 NRN ABE	AGATTGT ATAAAAG GCTGGGG GC	2945	AGAUUGUA UAAAAGGC UGGG	3251	GGC
GuideDesign90_CBE_NRN_20nt_3-9_022+_31946058_spCas9	TATA box	CBE_NRN_20nt_3-9_022	spCas9 NRN CBE	AGATTGT ATAAAAG GCTGGGG GC	2946	AGAUUGUA UAAAAGGC UGGG	3252	GGC
GuideDesign90_MBE_NRN_20nt_3-9_023+_31946058_spCas9	TATA box	MBE_NRN_20nt_3-9_023	spCas9 NRN MBE	AGATTGT ATAAAAG GCTGGGG GC	2947	AGAUUGUA UAAAAGGC UGGG	3253	GGC
GuideDesign90_ABE_NRCH_20nt_3-9_024+_31946058_spCas9	TATA box	ABE_NRCH_20nt_3-9_024	spCas9 NRCH ABE	AGATTGT ATAAAAG GCTGGGG GCT	2948	AGAUUGUA UAAAAGGC UGGG	3254	GGCT
GuideDesign90_CBE_NRCH_20nt_3-9_030+_31946058_spCas9	TATA box	CBE_NRCH_20nt_3-9_030	spCas9 NRCH CBE	AGATTGT ATAAAAG GCTGGGG GCT	2949	AGAUUGUA UAAAAGGC UGGG	3255	GGCT
GuideDesign90_CBE_NNN_RRT_21nt_3-12_015+_31946058_saCas9	TATA box	CBE_NNN_RRT_21nt_3-12_015	saCas9 KKH CBE	AGATTGT ATAAAAG GCTGGGG GCTGGT	2950	AGAUUGUA UAAAAGGC UGGGG	3256	GCTGGT
GuideDesign90_ABE_NGG_20nt_3-12_018+_31946065_spCas9	TATA box	ABE_NGG_20nt_3-12_018	spCas9 IBE	ATAAAAG GCTGGGG GCTGGTGG	2951	AUAAAAGG CUGGGGGC UGGU	3257	GGG
GuideDesign90_CBE_NGG_20nt_4-9_003+_31946065_spCas9	TATA box	CBE_NGG_20nt_4-9_003	spCas9 CBE	ATAAAAG GCTGGGG GCTGGTGG	2952	AUAAAAGG CUGGGGGC UGGU	3258	GGG
GuideDesign90_CBE_NGG_20nt_3-9_029+_31946065_spCas9	TATA box	CBE_NGG_20nt_3-9_029	spCas9 NGG CBE	ATAAAAG GCTGGGG GCTGGTGG	2953	AUAAAAGG CUGGGGGC UGGU	3259	GGG
GuideDesign90_CBE_NGG_20nt_3-16_033+_31946065_SpCas9	TATA box	CBE_NGG_20nt_3-16_033	SpCas9 IBE CBE	ATAAAAG GCTGGGG GCTGGTGG	2954	AUAAAAGG CUGGGGGC UGGU	3260	GGG

Guide polynucleotide name	Target site description	Editor	Cas description	Target Site	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
GuideDesign90_ABE_NG_20nt_3-9_027+_31946065_spCas9	TATA box	ABE_NG_20nt_3-9_027	spCas9 NG ABE	ATAAAAG GCTGGGG GCTGGTG G	2955	AUAAAAGG CUGGGGGC UGGU	3261	GG
GuideDesign90_CBE_NG_20nt_4-9_028+_31946065_spCas9	TATA box	CBE_NG_20nt_4-9_028	spCas9 NG CBE	ATAAAAG GCTGGGG GCTGGTG G	2956	AUAAAAGG CUGGGGGC UGGU	3262	GG
GuideDesign90_ABE_NRN_20nt_3-9_021+_31946065_spCas9	TATA box	ABE_NRN_20nt_3-9_021	spCas9 NRN ABE	ATAAAAG GCTGGGG GCTGGTG GG	2957	AUAAAAGG CUGGGGGC UGGU	3263	GGG
GuideDesign90_CBE_NRN_20nt_3-9_022+_31946065_spCas9	TATA box	CBE_NRN_20nt_3-9_022	spCas9 NRN CBE	ATAAAAG GCTGGGG GCTGGTG GG	2958	AUAAAAGG CUGGGGGC UGGU	3264	GGG
GuideDesign90_MBE_NRN_20nt_3-9_023+_31946065_spCas9	TATA box	MBE_NRN_20nt_3-9_023	spCas9 NRN MBE	ATAAAAG GCTGGGG GCTGGTG GG	2959	AUAAAAGG CUGGGGGC UGGU	3265	GGG
GuideDesign90_ABE_NGC_20nt_3-12_020-_31946039_spCas9	TATA box	ABE_NGC_20nt_3-12_020	spCas9 NGC IBE	ATCTGTG TTCTGGC ACCTGCG GC	2960	AUCUGUGU UCUGGCAC CUGC	3266	GGC
GuideDesign90_CBE_NGC_20nt_4-9_009-_31946039_spCas9	TATA box	CBE_NGC_20nt_4-9_009	spCas9 NGC CBE	ATCTGTG TTCTGGC ACCTGCG GC	2961	AUCUGUGU UCUGGCAC CUGC	3267	GGC
GuideDesign90_ABE_NG_20nt_3-9_027-_31946040_spCas9	TATA box	ABE_NG_20nt_3-9_027	spCas9 NG ABE	ATCTGTG TTCTGGC ACCTGCG G	2962	AUCUGUGU UCUGGCAC CUGC	3268	GG
GuideDesign90_CBE_NG_20nt_4-9_028-_31946040_spCas9	TATA box	CBE_NG_20nt_4-9_028	spCas9 NG CBE	ATCTGTG TTCTGGC ACCTGCG G	2963	AUCUGUGU UCUGGCAC CUGC	3269	GG
GuideDesign90_ABE_NRN_20nt_3-9_021	TATA box	ABE_NRN_20nt_3-9_021	spCas9 NRN ABE	ATCTGTG TTCTGGC	2964	AUCUGUGU UCUGGCAC CUGC	3270	GGC

Guide polynucleotide name	Target site description	Editor	Cas description	Target Site	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
9_021_- _31946039_sp Cas9				ACCTGCG GC				
GuideDesign9 0_CBE_NRN_ 20nt_3- 9_022_- _31946039_sp Cas9	TATA box	CBE_NRN _20nt_3- 9_022	spCas9 NRN CBE	ATCTGTG TTCTGGC ACCTGCG GC	2965	AUCUGUGU UCUGGCAC CUGC	3271	GGC
GuideDesign9 0_MBE_NRN _20nt_3- 9_023_- _31946039_sp Cas9	TATA box	MBE_NRN _20nt_3- 9_023	spCas9 NRN MBE	ATCTGTG TTCTGGC ACCTGCG GC	2966	AUCUGUGU UCUGGCAC CUGC	3272	GGC
GuideDesign9 0_ABE_NRC H_20nt_3- 9_024_- _31946038_sp Cas9	TATA box	ABE_NRC H_20nt_3- 9_024	spCas9 NRCH ABE	ATCTGTG TTCTGGC ACCTGCG GCT	2967	AUCUGUGU UCUGGCAC CUGC	3273	GGCT
GuideDesign9 0_CBE_NRC H_20nt_3- 9_030_- _31946038_sp Cas9	TATA box	CBE_NRC H_20nt_3- 9_030	spCas9 NRCH CBE	ATCTGTG TTCTGGC ACCTGCG GCT	2968	AUCUGUGU UCUGGCAC CUGC	3274	GGCT
GuideDesign9 0_ABE_NGG_ 20nt_3- 12_018_+_319 46055_spCas9	TATA box	ABE_NG G_20nt_3- 12_018	spCas9 IBE	CACAGAT TGTATAA AAGGCTG GG	2969	CACAGAUU GUAUAAAA GGCU	3275	GGG
GuideDesign9 0_ABE_NGG_ 20nt_13- 16_032_+_319 46055_SpCas9	TATA box	ABE_NG G_20nt_13- 16_032	SpCas9 IBE_ex panded ABE	CACAGAT TGTATAA AAGGCTG GG	2970	CACAGAUU GUAUAAAA GGCU	3276	GGG
GuideDesign9 0_CBE_NGG_ 20nt_4- 9_003_+_3194 6055_spCas9	TATA box	CBE_NGG _20nt_4- 9_003	spCas9 CBE	CACAGAT TGTATAA AAGGCTG GG	2971	CACAGAUU GUAUAAAA GGCU	3277	GGG
GuideDesign9 0_CBE_NGG_ 20nt_3- 9_029_+_3194 6055_spCas9	TATA box	CBE_NGG _20nt_3- 9_029	spCas9 NGG CBE	CACAGAT TGTATAA AAGGCTG GG	2972	CACAGAUU GUAUAAAA GGCU	3278	GGG
GuideDesign9 0_CBE_NGG_ 20nt_3- 16_033	TATA box	CBE_NGG _20nt_3- 16_033	SpCas9 IBE CBE	CACAGAT TGTATAA	2973	CACAGAUU GUAUAAAA GGCU	3279	GGG

Guide polynucleotide name	Target site description	Editor	Cas description	Target Site	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
16_033+_31946055_SpCas9				AAGGCTGG				
GuideDesign90_ABE_NG_20nt_3-9_027+_31946055_spCas9	TATA box	ABE_NG_20nt_3-9_027	spCas9_NG_ABE	CACAGATGTGTATAAAAGGCTGG	2974	CACAGAUUGUAUAAAAAGGCU	3280	GG
GuideDesign90_CBE_NG_20nt_4-9_028+_31946055_spCas9	TATA box	CBE_NG_20nt_4-9_028	spCas9_NG_CBE	CACAGATGTGTATAAAAGGCTGG	2975	CACAGAUUGUAUAAAAAGGCU	3281	GG
GuideDesign90_ABE_NRN_20nt_3-9_021+_31946055_spCas9	TATA box	ABE_NRN_20nt_3-9_021	spCas9_NRN_ABE	CACAGATGTGTATAAAAGGCTGG	2976	CACAGAUUGUAUAAAAAGGCU	3282	GGG
GuideDesign90_CBE_NRN_20nt_3-9_022+_31946055_spCas9	TATA box	CBE_NRN_20nt_3-9_022	spCas9_NRN_CBE	CACAGATGTGTATAAAAGGCTGG	2977	CACAGAUUGUAUAAAAAGGCU	3283	GGG
GuideDesign90_MBE_NRN_20nt_3-9_023+_31946055_spCas9	TATA box	MBE_NRN_20nt_3-9_023	spCas9_NRN_MBE	CACAGATGTGTATAAAAGGCTGG	2978	CACAGAUUGUAUAAAAAGGCU	3284	GGG
GuideDesign90_ABE_NGG_20nt_3-12_018+_31946050_spCas9	TATA box	ABE_NGG_20nt_3-12_018	spCas9_IBE	CAGAACA CAGATTGTATAAAAGG	2979	CAGAACACAGAUUGUAUAAA	3285	AGG
GuideDesign90_ABE_NGG_20nt_13-16_032+_31946050_SpCas9	TATA box	ABE_NGG_20nt_13-16_032	SpCas9_IBE_expanded_ABE	CAGAACA CAGATTGTATAAAAGG	2980	CAGAACACAGAUUGUAUAAA	3286	AGG
GuideDesign90_CBE_NGG_20nt_4-9_003+_31946050_spCas9	TATA box	CBE_NGG_20nt_4-9_003	spCas9_CBE	CAGAACA CAGATTGTATAAAAGG	2981	CAGAACACAGAUUGUAUAAA	3287	AGG
GuideDesign90_CBE_NGG_20nt_3-9_029+_31946050_spCas9	TATA box	CBE_NGG_20nt_3-9_029	spCas9_NGG_CBE	CAGAACA CAGATTGTATAAAAGG	2982	CAGAACACAGAUUGUAUAAA	3288	AGG
GuideDesign90_CBE_NGG_20nt_3-16_033	TATA box	CBE_NGG_20nt_3-16_033	SpCas9_IBE_CBE	CAGAACA CAGATTGTATAAAAGG	2983	CAGAACACAGAUUGUAUAAA	3289	AGG

Guide polynucleotide name	Target site description	Editor	Cas description	Target Site	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
16_033+_31946050_SpCas9				TATAAAAGG				
GuideDesign90_ABE_NG_20nt_3-9_027+_31946050_spCas9	TATA box	ABE_NG_20nt_3-9_027	spCas9_NG_ABE	CAGAACA CAGATTG TATAAAAG	2984	CAGAACAC AGAUUGUA UAAA	3290	AG
GuideDesign90_CBE_NG_20nt_4-9_028+_31946050_spCas9	TATA box	CBE_NG_20nt_4-9_028	spCas9_NG_CBE	CAGAACA CAGATTG TATAAAAG	2985	CAGAACAC AGAUUGUA UAAA	3291	AG
GuideDesign90_ABE_NRN_20nt_3-9_021+_31946050_spCas9	TATA box	ABE_NRN_20nt_3-9_021	spCas9_NRN_ABE	CAGAACA CAGATTG TATAAAAGG	2986	CAGAACAC AGAUUGUA UAAA	3292	AGG
GuideDesign90_CBE_NRN_20nt_3-9_022+_31946050_spCas9	TATA box	CBE_NRN_20nt_3-9_022	spCas9_NRN_CBE	CAGAACA CAGATTG TATAAAAGG	2987	CAGAACAC AGAUUGUA UAAA	3293	AGG
GuideDesign90_MBE_NRN_20nt_3-9_023+_31946050_spCas9	TATA box	MBE_NRN_20nt_3-9_023	spCas9_NRN_MBE	CAGAACA CAGATTG TATAAAAGG	2988	CAGAACAC AGAUUGUA UAAA	3294	AGG
GuideDesign90_CBE_NRRH_20nt_3-9_031+_31946050_spCas9	TATA box	CBE_NRRH_20nt_3-9_031	spCas9_NRRH_CBE	CAGAACA CAGATTG TATAAAAGGC	2989	CAGAACAC AGAUUGUA UAAA	3295	AGGC
GuideDesign90_ABE_NGG_20nt_3-12_018+_31946057_spCas9	TATA box	ABE_NG_20nt_3-12_018	spCas9_IBE	CAGATTG TATAAAAGGCTGGGG	2990	CAGAUUGU AUAAGG CUGG	3296	GGG
GuideDesign90_ABE_NGG_20nt_13-16_032+_31946057_SpCas9	TATA box	ABE_NG_20nt_13-16_032	SpCas9_IBE_expanded_ABE	CAGATTG TATAAAAGGCTGGGG	2991	CAGAUUGU AUAAGG CUGG	3297	GGG
GuideDesign90_CBE_NGG_20nt_4-9_003+_31946057_spCas9	TATA box	CBE_NGG_20nt_4-9_003	spCas9_CBE	CAGATTG TATAAAAGGCTGGGG	2992	CAGAUUGU AUAAGG CUGG	3298	GGG
GuideDesign90_CBE_NGG_20nt_3-9_029	TATA box	CBE_NGG_20nt_3-9_029	spCas9_NGG_CBE	CAGATTG TATAAAAGG	2993	CAGAUUGU AUAAGG CUGG	3299	GGG

Guide polynucleotide name	Target site description	Editor	Cas description	Target Site	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
9_029_+_31946057_spCas9				GGCTGGGGG				
GuideDesign90_CBE_NGG_20nt_3-16_033_+_31946057_SpCas9	TATA box	CBE_NGG_20nt_3-16_033	SpCas9 IBE CBE	CAGATTG TATAAAA GGCTGGGGG	2994	CAGAUUGU AUAAGG CUGG	3300	GGG
GuideDesign90_ABE_NG_20nt_3-9_027_+_31946057_spCas9	TATA box	ABE_NG_20nt_3-9_027	spCas9 NG ABE	CAGATTG TATAAAA GGCTGGGG	2995	CAGAUUGU AUAAGG CUGG	3301	GG
GuideDesign90_CBE_NG_20nt_4-9_028_+_31946057_spCas9	TATA box	CBE_NG_20nt_4-9_028	spCas9 NG CBE	CAGATTG TATAAAA GGCTGGGG	2996	CAGAUUGU AUAAGG CUGG	3302	GG
GuideDesign90_ABE_NRN_20nt_3-9_021_+_31946057_spCas9	TATA box	ABE_NRN_20nt_3-9_021	spCas9 NRN ABE	CAGATTG TATAAAA GGCTGGGG	2997	CAGAUUGU AUAAGG CUGG	3303	GGG
GuideDesign90_CBE_NRN_20nt_3-9_022_+_31946057_spCas9	TATA box	CBE_NRN_20nt_3-9_022	spCas9 NRN CBE	CAGATTG TATAAAA GGCTGGGG	2998	CAGAUUGU AUAAGG CUGG	3304	GGG
GuideDesign90_MBE_NRN_20nt_3-9_023_+_31946057_spCas9	TATA box	MBE_NRN_20nt_3-9_023	spCas9 NRN MBE	CAGATTG TATAAAA GGCTGGGG	2999	CAGAUUGU AUAAGG CUGG	3305	GGG
GuideDesign90_CBE_NRRH_20nt_3-9_031_+_31946057_spCas9	TATA box	CBE_NRRH_20nt_3-9_031	spCas9 NRRH CBE	CAGATTG TATAAAA GGCTGGGGG	3000	CAGAUUGU AUAAGG CUGG	3306	GGGC
GuideDesign90_ABE_NRN_20nt_3-9_021_-31946060_spCas9	TATA box	ABE_NRN_20nt_3-9_021	spCas9 NRN ABE	CAGCCCC CAGCCTT TTATACAT	3001	CAGCCCCC AGCCUUUU AUAC	3307	AAT
GuideDesign90_CBE_NRN_20nt_3-9_022_-31946060_spCas9	TATA box	CBE_NRN_20nt_3-9_022	spCas9 NRN CBE	CAGCCCC CAGCCTT TTATACAT	3002	CAGCCCCC AGCCUUUU AUAC	3308	AAT

Guide polynucleotide name	Target site description	Editor	Cas description	Target Site	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
GuideDesign90_MBE_NRN_20nt_3-9_023 -_31946060_sp_Cas9	TATA box	MBE_NRN_20nt_3-9_023	spCas9 NRN MBE	CAGCCCC CAGCCTT TTATACAT	3003	CAGCCCCC AGCCUUUU AUAC	3309	AAT
GuideDesign90_ABE_NRT_H_20nt_3-9_025 -_31946059_sp_Cas9	TATA box	ABE_NRT_H_20nt_3-9_025	spCas9 NRTH ABE	CAGCCCC CAGCCTT TTATACATC	3004	CAGCCCCC AGCCUUUU AUAC	3310	AATC
GuideDesign90_CBE_NRTH_20nt_4-9_026 -_31946059_sp_Cas9	TATA box	CBE_NRT_H_20nt_4-9_026	spCas9 NRTH CBE	CAGCCCC CAGCCTT TTATACATC	3005	CAGCCCCC AGCCUUUU AUAC	3311	AATC
GuideDesign90_CBE_NNN_RRT_21nt_3-12_015 -_31946060_sa_Cas9	TATA box	CBE_NNN_RRT_21nt_3-12_015	saCas9 KKH CBE	CCACCAG CCCCAG CCTTTTA TACAAT	3006	CCACCAGC CCCCAGCC UUUUA	3312	TACAAT
GuideDesign90_ABE_NRN_20nt_3-9_021 -_31946061_sp_Cas9	TATA box	ABE_NRN_20nt_3-9_021	spCas9 NRN ABE	CCAGCCC CCAGCCT TTTATACAA	3007	CCAGCCCC CAGCCUUU UAUA	3313	CAA
GuideDesign90_CBE_NRN_20nt_3-9_022 -_31946061_sp_Cas9	TATA box	CBE_NRN_20nt_3-9_022	spCas9 NRN CBE	CCAGCCC CCAGCCT TTTATACAA	3008	CCAGCCCC CAGCCUUU UAUA	3314	CAA
GuideDesign90_MBE_NRN_20nt_3-9_023 -_31946061_sp_Cas9	TATA box	MBE_NRN_20nt_3-9_023	spCas9 NRN MBE	CCAGCCC CCAGCCT TTTATACAA	3009	CCAGCCCC CAGCCUUU UAUA	3315	CAA
GuideDesign90_CBE_NRR_H_20nt_3-9_031 -_31946060_sp_Cas9	TATA box	CBE_NRR_H_20nt_3-9_031	spCas9 NRRH CBE	CCAGCCC CCAGCCT TTTATAC AAT	3010	CCAGCCCC CAGCCUUU UAUA	3316	CAAT

Guide polynucleotide name	Target site description	Editor	Cas description	Target Site	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
GuideDesign90_ABE_NG_20nt_3-9_027_-31946055_sp_Cas9	TATA box	ABE_NG_20nt_3-9_027	spCas9 NG ABE	CCAGCCTTTTATAC AATCTGTG	3011	CCAGCCUUUUAUACAAUCUG	3317	TG
GuideDesign90_CBE_NG_20nt_4-9_028_-31946055_sp_Cas9	TATA box	CBE_NG_20nt_4-9_028	spCas9 NG CBE	CCAGCCTTTTATAC AATCTGTG	3012	CCAGCCUUUUAUACAAUCUG	3318	TG
GuideDesign90_ABE_NRN_20nt_3-9_021_-31946054_sp_Cas9	TATA box	ABE_NRN_20nt_3-9_021	spCas9 NRN ABE	CCAGCCTTTTATAC AATCTGTGT	3013	CCAGCCUUUUAUACAAUCUG	3319	TGT
GuideDesign90_CBE_NRN_20nt_3-9_022_-31946054_sp_Cas9	TATA box	CBE_NRN_20nt_3-9_022	spCas9 NRN CBE	CCAGCCTTTTATAC AATCTGTGT	3014	CCAGCCUUUUAUACAAUCUG	3320	TGT
GuideDesign90_MBE_NRN_20nt_3-9_023_-31946054_sp_Cas9	TATA box	MBE_NRN_20nt_3-9_023	spCas9 NRN MBE	CCAGCCTTTTATAC AATCTGTGT	3015	CCAGCCUUUUAUACAAUCUG	3321	TGT
GuideDesign90_ABE_NRTH_20nt_3-9_025_-31946053_sp_Cas9	TATA box	ABE_NRTH_20nt_3-9_025	spCas9 NRTH ABE	CCAGCCTTTTATAC AATCTGTGTT	3016	CCAGCCUUUUAUACAAUCUG	3322	TGTT
GuideDesign90_CBE_NRTH_20nt_4-9_026_-31946053_sp_Cas9	TATA box	CBE_NRTH_20nt_4-9_026	spCas9 NRTH CBE	CCAGCCTTTTATAC AATCTGTGTT	3017	CCAGCCUUUUAUACAAUCUG	3323	TGTT
GuideDesign90_ABE_NG_20nt_3-9_027_-31946057_sp_Cas9	TATA box	ABE_NG_20nt_3-9_027	spCas9 NG ABE	CCCCAGCCTTTTATAC AATCTGTG	3018	CCCCAGCCUUUUUAUACAAUC	3324	TG
GuideDesign90_CBE_NG_20nt_4-9_028_-31946057_sp_Cas9	TATA box	CBE_NG_20nt_4-9_028	spCas9 NG CBE	CCCCAGCCTTTTATAC AATCTGTG	3019	CCCCAGCCUUUUUAUACAAUC	3325	TG

Guide polynucleotide name	Target site description	Editor	Cas description	Target Site	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
GuideDesign90_ABE_NRN_20nt_3-9_021_-31946056_spCas9	TATA box	ABE_NRN_20nt_3-9_021	spCas9 NRN ABE	CCCCAGCCTTTTATACAATCTGT	3020	CCCCAGCCUUUUUAUACAAUC	3326	TGT
GuideDesign90_CBE_NRN_20nt_3-9_022_-31946056_spCas9	TATA box	CBE_NRN_20nt_3-9_022	spCas9 NRN CBE	CCCCAGCCTTTTATACAATCTGT	3021	CCCCAGCCUUUUUAUACAAUC	3327	TGT
GuideDesign90_MBE_NRN_20nt_3-9_023_-31946056_spCas9	TATA box	MBE_NRN_20nt_3-9_023	spCas9 NRN MBE	CCCCAGCCTTTTATACAATCTGT	3022	CCCCAGCCUUUUUAUACAAUC	3328	TGT
GuideDesign90_ABE_NGG_20nt_3-9_002_+31946073_spCas9	TATA box	ABE_NGG_20nt_3-9_002	spCas9 ABE	CTGGGGGCTGGTGGGGAGCAGGG	3023	CUGGGGGCUGGUGGGGAGCA	3329	GGG
GuideDesign90_ABE_NGG_20nt_3-12_018_+31946073_spCas9	TATA box	ABE_NGG_20nt_3-12_018	spCas9 IBE	CTGGGGGCTGGTGGGGAGCAGGG	3024	CUGGGGGCUGGUGGGGAGCA	3330	GGG
GuideDesign90_CBE_NGG_20nt_4-9_003_+31946073_spCas9	TATA box	CBE_NGG_20nt_4-9_003	spCas9 CBE	CTGGGGGCTGGTGGGGAGCAGGG	3025	CUGGGGGCUGGUGGGGAGCA	3331	GGG
GuideDesign90_CBE_NGG_20nt_3-9_029_+31946073_spCas9	TATA box	CBE_NGG_20nt_3-9_029	spCas9 NGG CBE	CTGGGGGCTGGTGGGGAGCAGGG	3026	CUGGGGGCUGGUGGGGAGCA	3332	GGG
GuideDesign90_CBE_NGG_20nt_3-16_033_+31946073_SpCas9	TATA box	CBE_NGG_20nt_3-16_033	SpCas9 IBE CBE	CTGGGGGCTGGTGGGGAGCAGGG	3027	CUGGGGGCUGGUGGGGAGCA	3333	GGG
GuideDesign90_ABE_NG_20nt_3-9_027_+31946073_spCas9	TATA box	ABE_NG_20nt_3-9_027	spCas9 NG ABE	CTGGGGGCTGGTGGGGAGCAGG	3028	CUGGGGGCUGGUGGGGAGCA	3334	GG

Guide polynucleotide name	Target site description	Editor	Cas description	Target Site	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
GuideDesign90_CBE_NG_20nt_4-9_028+_31946073_spCas9	TATA box	CBE_NG_20nt_4-9_028	spCas9 NG CBE	CTGGGGG CTGGTGG GGAGCAGG	3029	CUGGGGGC UGGUGGGG AGCA	3335	GG
GuideDesign90_ABE_NRN_20nt_3-9_021+_31946073_spCas9	TATA box	ABE_NRN_20nt_3-9_021	spCas9 NRN ABE	CTGGGGG CTGGTGG GGAGCAGG	3030	CUGGGGGC UGGUGGGG AGCA	3336	GGG
GuideDesign90_CBE_NRN_20nt_3-9_022+_31946073_spCas9	TATA box	CBE_NRN_20nt_3-9_022	spCas9 NRN CBE	CTGGGGG CTGGTGG GGAGCAGG	3031	CUGGGGGC UGGUGGGG AGCA	3337	GGG
GuideDesign90_MBE_NRN_20nt_3-9_023+_31946073_spCas9	TATA box	MBE_NRN_20nt_3-9_023	spCas9 NRN MBE	CTGGGGG CTGGTGG GGAGCAGG	3032	CUGGGGGC UGGUGGGG AGCA	3338	GGG
GuideDesign90_ABE_NGG_20nt_3-12_018-_31946049_spCas9	TATA box	ABE_NG_20nt_3-12_018	spCas9 IBE	CTTTTAT ACAATCT GTGTTCT GG	3033	CUUUUAUA CAAUCUGU GUUC	3339	TGG
GuideDesign90_ABE_NGG_20nt_13-16_032-_31946049_SpCas9	TATA box	ABE_NG_20nt_13-16_032	SpCas9 IBE_expanded ABE	CTTTTAT ACAATCT GTGTTCT GG	3034	CUUUUAUA CAAUCUGU GUUC	3340	TGG
GuideDesign90_CBE_NGG_20nt_4-9_003-_31946049_spCas9	TATA box	CBE_NGG_20nt_4-9_003	spCas9 CBE	CTTTTAT ACAATCT GTGTTCT GG	3035	CUUUUAUA CAAUCUGU GUUC	3341	TGG
GuideDesign90_CBE_NGG_20nt_3-9_029-_31946049_spCas9	TATA box	CBE_NGG_20nt_3-9_029	spCas9 NGG CBE	CTTTTAT ACAATCT GTGTTCT GG	3036	CUUUUAUA CAAUCUGU GUUC	3342	TGG
GuideDesign90_CBE_NGG_20nt_3-16_033-_31946049_SpCas9	TATA box	CBE_NGG_20nt_3-16_033	SpCas9 IBE CBE	CTTTTAT ACAATCT GTGTTCT GG	3037	CUUUUAUA CAAUCUGU GUUC	3343	TGG

Guide polynucleotide name	Target site description	Editor	Cas description	Target Site	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
GuideDesign90_ABE_NG_20nt_3-9_027_-31946050_spCas9	TATA box	ABE_NG_20nt_3-9_027	spCas9 NG ABE	CTTTTATACAATCTGTGTTCTG	3038	CUUUUAUACAAUCUGUGUUC	3344	TG
GuideDesign90_CBE_NG_20nt_4-9_028_-31946050_spCas9	TATA box	CBE_NG_20nt_4-9_028	spCas9 NG CBE	CTTTTATACAATCTGTGTTCTG	3039	CUUUUAUACAAUCUGUGUUC	3345	TG
GuideDesign90_ABE_NRN_20nt_3-9_021_-31946049_spCas9	TATA box	ABE_NRN_20nt_3-9_021	spCas9 NRN ABE	CTTTTATACAATCTGTGTTCTGG	3040	CUUUUAUACAAUCUGUGUUC	3346	TGG
GuideDesign90_CBE_NRN_20nt_3-9_022_-31946049_spCas9	TATA box	CBE_NRN_20nt_3-9_022	spCas9 NRN CBE	CTTTTATACAATCTGTGTTCTGG	3041	CUUUUAUACAAUCUGUGUUC	3347	TGG
GuideDesign90_MBE_NRN_20nt_3-9_023_-31946049_spCas9	TATA box	MBE_NRN_20nt_3-9_023	spCas9 NRN MBE	CTTTTATACAATCTGTGTTCTGG	3042	CUUUUAUACAAUCUGUGUUC	3348	TGG
GuideDesign90_CBE_NRRH_20nt_3-9_031_-31946048_spCas9	TATA box	CBE_NRRH_20nt_3-9_031	spCas9 NRRH CBE	CTTTTATACAATCTGTGTTCTGGC	3043	CUUUUAUACAAUCUGUGUUC	3349	TGGC
GuideDesign90_ABE_NGG_20nt_3-9_002_+31946072_spCas9	TATA box	ABE_NGG_20nt_3-9_002	spCas9 ABE	GCTGGGGGCTGGGTGGGGAGCAGG	3044	GCUGGGGGCUGGUGGGGAGC	3350	AGG
GuideDesign90_ABE_NGG_20nt_3-12_018_+31946072_spCas9	TATA box	ABE_NGG_20nt_3-12_018	spCas9 IBE	GCTGGGGGCTGGGTGGGGAGCAGG	3045	GCUGGGGGCUGGUGGGGAGC	3351	AGG
GuideDesign90_CBE_NGG_20nt_4-9_003_+31946072_spCas9	TATA box	CBE_NGG_20nt_4-9_003	spCas9 CBE	GCTGGGGGCTGGGTGGGGAGCAGG	3046	GCUGGGGGCUGGUGGGGAGC	3352	AGG

Guide polynucleotide name	Target site description	Editor	Cas description	Target Site	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
GuideDesign90_CBE_NGG_20nt_3-9_029_+31946072_spCas9	TATA box	CBE_NGG_20nt_3-9_029	spCas9_NGG_CBE	GCTGGGGG GCTGGGTG GGGAGCAGG	3047	GCUGGGGG CUGGUGGG GAGC	3353	AGG
GuideDesign90_CBE_NGG_20nt_3-16_033_+31946072_SpCas9	TATA box	CBE_NGG_20nt_3-16_033	SpCas9_IBE_CBE	GCTGGGGG GCTGGGTG GGGAGCAGG	3048	GCUGGGGG CUGGUGGG GAGC	3354	AGG
GuideDesign90_ABE_NG_20nt_3-9_027_+31946072_spCas9	TATA box	ABE_NG_20nt_3-9_027	spCas9_NG_ABE	GCTGGGGG GCTGGGTG GGGAGCAG	3049	GCUGGGGG CUGGUGGG GAGC	3355	AG
GuideDesign90_CBE_NG_20nt_4-9_028_+31946072_spCas9	TATA box	CBE_NG_20nt_4-9_028	spCas9_NG_CBE	GCTGGGGG GCTGGGTG GGGAGCAG	3050	GCUGGGGG CUGGUGGG GAGC	3356	AG
GuideDesign90_ABE_NRN_20nt_3-9_021_+31946072_spCas9	TATA box	ABE_NRN_20nt_3-9_021	spCas9_NRN_ABE	GCTGGGGG GCTGGGTG GGGAGCAGG	3051	GCUGGGGG CUGGUGGG GAGC	3357	AGG
GuideDesign90_CBE_NRN_20nt_3-9_022_+31946072_spCas9	TATA box	CBE_NRN_20nt_3-9_022	spCas9_NRN_CBE	GCTGGGGG GCTGGGTG GGGAGCAGG	3052	GCUGGGGG CUGGUGGG GAGC	3358	AGG
GuideDesign90_MBE_NRN_20nt_3-9_023_+31946072_spCas9	TATA box	MBE_NRN_20nt_3-9_023	spCas9_NRN_MBE	GCTGGGGG GCTGGGTG GGGAGCAGG	3053	GCUGGGGG CUGGUGGG GAGC	3359	AGG
GuideDesign90_ABE_NRN_20nt_3-9_021_+31946071_spCas9	TATA box	ABE_NRN_20nt_3-9_021	spCas9_NRN_ABE	GGCTGGG GGCTGGT GGGGAGCAG	3054	GGCUGGGG GCUGGUGG GGAG	3360	CAG
GuideDesign90_CBE_NRN_20nt_3-9_022_+31946071_spCas9	TATA box	CBE_NRN_20nt_3-9_022	spCas9_NRN_CBE	GGCTGGG GGCTGGT GGGGAGCAG	3055	GGCUGGGG GCUGGUGG GGAG	3361	CAG
GuideDesign90_MBE_NRN_20nt_3-9_023_+31946071_spCas9	TATA box	MBE_NRN_20nt_3-9_023	spCas9_NRN_MBE	GGCTGGG GGCTGGT GGGGAGCAG	3056	GGCUGGGG GCUGGUGG GGAG	3362	CAG

Guide polynucleotide name	Target site description	Editor	Cas description	Target Site	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
GuideDesign90_ABE_NGG_20nt_3-12_018_+_31946066_spCas9	TATA box	ABE_NGG_20nt_3-12_018	spCas9 IBE	TAAAAGGCTGGGGGCTGGTGGG	3057	UAAAAGGCUGGGGGCGGUG	3363	GGG
GuideDesign90_CBE_NGG_20nt_4-9_003_+_31946066_spCas9	TATA box	CBE_NGG_20nt_4-9_003	spCas9 CBE	TAAAAGGCTGGGGGCTGGTGGG	3058	UAAAAGGCUGGGGGCGGUG	3364	GGG
GuideDesign90_CBE_NGG_20nt_3-9_029_+_31946066_spCas9	TATA box	CBE_NGG_20nt_3-9_029	spCas9 NGG CBE	TAAAAGGCTGGGGGCTGGTGGG	3059	UAAAAGGCUGGGGGCGGUG	3365	GGG
GuideDesign90_CBE_NGG_20nt_3-16_033_+_31946066_SpCas9	TATA box	CBE_NGG_20nt_3-16_033	SpCas9 IBE CBE	TAAAAGGCTGGGGGCTGGTGGG	3060	UAAAAGGCUGGGGGCGGUG	3366	GGG
GuideDesign90_ABE_NG_20nt_3-9_027_+_31946066_spCas9	TATA box	ABE_NG_20nt_3-9_027	spCas9 NG ABE	TAAAAGGCTGGGGGCTGGTGGG	3061	UAAAAGGCUGGGGGCGGUG	3367	GG
GuideDesign90_CBE_NG_20nt_4-9_028_+_31946066_spCas9	TATA box	CBE_NG_20nt_4-9_028	spCas9 NG CBE	TAAAAGGCTGGGGGCTGGTGGG	3062	UAAAAGGCUGGGGGCGGUG	3368	GG
GuideDesign90_ABE_NRN_20nt_3-9_021_+_31946066_spCas9	TATA box	ABE_NRN_20nt_3-9_021	spCas9 NRN ABE	TAAAAGGCTGGGGGCTGGTGGG	3063	UAAAAGGCUGGGGGCGGUG	3369	GGG
GuideDesign90_CBE_NRN_20nt_3-9_022_+_31946066_spCas9	TATA box	CBE_NRN_20nt_3-9_022	spCas9 NRN CBE	TAAAAGGCTGGGGGCTGGTGGG	3064	UAAAAGGCUGGGGGCGGUG	3370	GGG
GuideDesign90_MBE_NRN_20nt_3-9_023_+_31946066_spCas9	TATA box	MBE_NRN_20nt_3-9_023	spCas9 NRN MBE	TAAAAGGCTGGGGGCTGGTGGG	3065	UAAAAGGCUGGGGGCGGUG	3371	GGG
GuideDesign90_CBE_NRRH_20nt_3-9_031_+_31946066_spCas9	TATA box	CBE_NRRH_20nt_3-9_031	spCas9 NRRH CBE	TAAAAGGCTGGGGGCTGGTGGGGA	3066	UAAAAGGCUGGGGGCGGUG	3372	GGGA

Guide polynucleotide name	Target site description	Editor	Cas description	Target Site	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
GuideDesign90_ABE_NGG_20nt_3-12_018+_31946064_spCas9	TATA box	ABE_NGG_20nt_3-12_018	spCas9 IBE	TATAAAA GGCTGGG GGCTGGT GG	3067	UAUAAAAG GCUGGGGG CUGG	3373	TGG
GuideDesign90_ABE_NGG_20nt_13-16_032+_31946064_SpCas9	TATA box	ABE_NGG_20nt_13-16_032	SpCas9 IBE_expanded ABE	TATAAAA GGCTGGG GGCTGGT GG	3068	UAUAAAAG GCUGGGGG CUGG	3374	TGG
GuideDesign90_CBE_NGG_20nt_4-9_003+_31946064_spCas9	TATA box	CBE_NGG_20nt_4-9_003	spCas9 CBE	TATAAAA GGCTGGG GGCTGGT GG	3069	UAUAAAAG GCUGGGGG CUGG	3375	TGG
GuideDesign90_CBE_NGG_20nt_3-9_029+_31946064_spCas9	TATA box	CBE_NGG_20nt_3-9_029	spCas9 NGG CBE	TATAAAA GGCTGGG GGCTGGT GG	3070	UAUAAAAG GCUGGGGG CUGG	3376	TGG
GuideDesign90_CBE_NGG_20nt_3-16_033+_31946064_SpCas9	TATA box	CBE_NGG_20nt_3-16_033	SpCas9 IBE CBE	TATAAAA GGCTGGG GGCTGGT GG	3071	UAUAAAAG GCUGGGGG CUGG	3377	TGG
GuideDesign90_ABE_NG_20nt_3-9_027+_31946064_spCas9	TATA box	ABE_NG_20nt_3-9_027	spCas9 NG ABE	TATAAAA GGCTGGG GGCTGGT G	3072	UAUAAAAG GCUGGGGG CUGG	3378	TG
GuideDesign90_CBE_NG_20nt_4-9_028+_31946064_spCas9	TATA box	CBE_NG_20nt_4-9_028	spCas9 NG CBE	TATAAAA GGCTGGG GGCTGGT G	3073	UAUAAAAG GCUGGGGG CUGG	3379	TG
GuideDesign90_ABE_NRN_20nt_3-9_021+_31946064_spCas9	TATA box	ABE_NRN_20nt_3-9_021	spCas9 NRN ABE	TATAAAA GGCTGGG GGCTGGT GG	3074	UAUAAAAG GCUGGGGG CUGG	3380	TGG
GuideDesign90_CBE_NRN_20nt_3-9_022+_31946064_spCas9	TATA box	CBE_NRN_20nt_3-9_022	spCas9 NRN CBE	TATAAAA GGCTGGG GGCTGGT GG	3075	UAUAAAAG GCUGGGGG CUGG	3381	TGG
GuideDesign90_MBE_NRN_20nt_3-9_023+_31946064_spCas9	TATA box	MBE_NRN_20nt_3-9_023	spCas9 NRN MBE	TATAAAA GGCTGGG GGCTGGT GG	3076	UAUAAAAG GCUGGGGG CUGG	3382	TGG

Guide polynucleotide name	Target site description	Editor	Cas description	Target Site	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
GuideDesign90_ABE_VTTN_22nt_5-9_017+_31946060_cas12b	TATA box	ABE_VTTN_22nt_5-9_017	cas12b ABE	ATTGTAT AAAAGGC TGGGGGC TGGTG	3077	UAUAAAAG GCUGGGGG CUGGUG	3383	ATTG
GuideDesign90_ABE_VTTN_22nt_5-9_017-_31946046_cas12b	TATA box	ABE_VTTN_22nt_5-9_017	cas12b ABE	CTTTTAT ACAATCT GTGTTCT GGCAC	3078	UAUACAAU CUGUGUUC UGGCAC	3384	CTTT
GuideDesign90_ABE_NGG_20nt_3-9_002+_31946074_spCas9	TATA box	ABE_NGG_20nt_3-9_002	spCas9 ABE	TGGGGGC TGGTGGG GAGCAGG GG	3079	UGGGGGCU GGUGGGGA GCAG	3385	GGG
GuideDesign90_ABE_NGG_20nt_3-12_018+_31946074_spCas9	TATA box	ABE_NGG_20nt_3-12_018	spCas9 IBE	TGGGGGC TGGTGGG GAGCAGG GG	3080	UGGGGGCU GGUGGGGA GCAG	3386	GGG
GuideDesign90_CBE_NGG_20nt_3-9_029+_31946074_spCas9	TATA box	CBE_NGG_20nt_3-9_029	spCas9 NGG CBE	TGGGGGC TGGTGGG GAGCAGG GG	3081	UGGGGGCU GGUGGGGA GCAG	3387	GGG
GuideDesign90_CBE_NGG_20nt_3-16_033+_31946074_SpCas9	TATA box	CBE_NGG_20nt_3-16_033	SpCas9 IBE CBE	TGGGGGC TGGTGGG GAGCAGG GG	3082	UGGGGGCU GGUGGGGA GCAG	3388	GGG
GuideDesign90_ABE_NG_20nt_3-9_027+_31946074_spCas9	TATA box	ABE_NG_20nt_3-9_027	spCas9 NG ABE	TGGGGGC TGGTGGG GAGCAGG G	3083	UGGGGGCU GGUGGGGA GCAG	3389	GG
GuideDesign90_ABE_NRN_20nt_3-9_021+_31946074_spCas9	TATA box	ABE_NRN_20nt_3-9_021	spCas9 NRN ABE	TGGGGGC TGGTGGG GAGCAGG GG	3084	UGGGGGCU GGUGGGGA GCAG	3390	GGG
GuideDesign90_CBE_NRN_20nt_3-9_022+_31946074_spCas9	TATA box	CBE_NRN_20nt_3-9_022	spCas9 NRN CBE	TGGGGGC TGGTGGG GAGCAGG GG	3085	UGGGGGCU GGUGGGGA GCAG	3391	GGG
GuideDesign90_MBE_NRN_20nt_3-9_023	TATA box	MBE_NRN_20nt_3-9_023	spCas9 NRN MBE	TGGGGGC TGGTGGG GAGCAGG GG	3086	UGGGGGCU GGUGGGGA GCAG	3392	GGG

Guide polynucleotide name	Target site description	Editor	Cas description	Target Site	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
9_023_+_31946074_spCas9								
GuideDesign90_ABE_NG_20nt_3-9_027_+_31946062_spCas9	TATA box	ABE_NG_20nt_3-9_027	spCas9_NG_ABE	TGTATAAAAGGCTGGGGGCTGG	3087	UGUAUAAAAGGCUGGGGCGU	3393	GG
GuideDesign90_CBE_NG_20nt_4-9_028_+_31946062_spCas9	TATA box	CBE_NG_20nt_4-9_028	spCas9_NG_CBE	TGTATAAAAGGCTGGGGGCTGG	3088	UGUAUAAAAGGCUGGGGCGU	3394	GG
GuideDesign90_ABE_NRN_20nt_3-9_021_+_31946062_spCas9	TATA box	ABE_NRN_20nt_3-9_021	spCas9_NRN_ABE	TGTATAAAAGGCTGGGGGCTGGT	3089	UGUAUAAAAGGCUGGGGCGU	3395	GGT
GuideDesign90_CBE_NRN_20nt_3-9_022_+_31946062_spCas9	TATA box	CBE_NRN_20nt_3-9_022	spCas9_NRN_CBE	TGTATAAAAGGCTGGGGGCTGGT	3090	UGUAUAAAAGGCUGGGGCGU	3396	GGT
GuideDesign90_MBE_NRN_20nt_3-9_023_+_31946062_spCas9	TATA box	MBE_NRN_20nt_3-9_023	spCas9_NRN_MBE	TGTATAAAAGGCTGGGGGCTGGT	3091	UGUAUAAAAGGCUGGGGCGU	3397	GGT
GuideDesign90_ABE_NRN_20nt_3-9_021_-_31946046_spCas9	TATA box	ABE_NRN_20nt_3-9_021	spCas9_NRN_ABE	TTATACAATCTGTGTTCTGGCAC	3092	UUAUACAAUCUGUGUUCUGG	3398	CAC
GuideDesign90_CBE_NRN_20nt_3-9_022_-_31946046_spCas9	TATA box	CBE_NRN_20nt_3-9_022	spCas9_NRN_CBE	TTATACAATCTGTGTTCTGGCAC	3093	UUAUACAAUCUGUGUUCUGG	3399	CAC
GuideDesign90_MBE_NRN_20nt_3-9_023_-_31946046_spCas9	TATA box	MBE_NRN_20nt_3-9_023	spCas9_NRN_MBE	TTATACAATCTGTGTTCTGGCAC	3094	UUAUACAAUCUGUGUUCUGG	3400	CAC
GuideDesign90_ABE_NRCH_20nt_3-9_024_-_	TATA box	ABE_NRCH_20nt_3-9_024	spCas9_NRCH_ABE	TTATACAATCTGTGTTCTGGCAC	3095	UUAUACAAUCUGUGUUCUGG	3401	CACC

Guide polynucleotide name	Target site description	Editor	Cas description	Target Site	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
_31946045_sp Cas9								
GuideDesign90_CBE_NRCH_20nt_3-9_030 -_31946045_sp Cas9	TATA box	CBE_NRCH_20nt_3-9_030	spCas9 NRCH CBE	TTATACA ATCTGTG TTCTGGC ACC	3096	UUAUACAA UCUGUGUU CUGG	3402	CACC
GuideDesign90_ABE_NGG_20nt_3-9_002+_31946061_spCas9	TATA box	ABE_NGG_20nt_3-9_002	spCas9 ABE	TTGTATA AAAGGCT GGGGGCT GG	3097	UUGUAUAA AAGGCUGG GGGC	3403	TGG
GuideDesign90_ABE_NGG_20nt_3-12_018+_31946061_spCas9	TATA box	ABE_NGG_20nt_3-12_018	spCas9 IBE	TTGTATA AAAGGCT GGGGGCT GG	3098	UUGUAUAA AAGGCUGG GGGC	3404	TGG
GuideDesign90_ABE_NGG_20nt_13-16_032+_31946061_SpCas9	TATA box	ABE_NGG_20nt_13-16_032	SpCas9 IBE_expanded ABE	TTGTATA AAAGGCT GGGGGCT GG	3099	UUGUAUAA AAGGCUGG GGGC	3405	TGG
GuideDesign90_CBE_NGG_20nt_4-9_003+_31946061_spCas9	TATA box	CBE_NGG_20nt_4-9_003	spCas9 CBE	TTGTATA AAAGGCT GGGGGCT GG	3100	UUGUAUAA AAGGCUGG GGGC	3406	TGG
GuideDesign90_CBE_NGG_20nt_3-9_029+_31946061_spCas9	TATA box	CBE_NGG_20nt_3-9_029	spCas9 NGG CBE	TTGTATA AAAGGCT GGGGGCT GG	3101	UUGUAUAA AAGGCUGG GGGC	3407	TGG
GuideDesign90_CBE_NGG_20nt_3-16_033+_31946061_SpCas9	TATA box	CBE_NGG_20nt_3-16_033	SpCas9 IBE CBE	TTGTATA AAAGGCT GGGGGCT GG	3102	UUGUAUAA AAGGCUGG GGGC	3408	TGG
GuideDesign90_ABE_NG_20nt_3-9_027+_31946061_spCas9	TATA box	ABE_NG_20nt_3-9_027	spCas9 NG ABE	TTGTATA AAAGGCT GGGGGCT G	3103	UUGUAUAA AAGGCUGG GGGC	3409	TG
GuideDesign90_CBE_NG_20nt_4-9_028+_31946061_spCas9	TATA box	CBE_NG_20nt_4-9_028	spCas9 NG CBE	TTGTATA AAAGGCT GGGGGCT G	3104	UUGUAUAA AAGGCUGG GGGC	3410	TG

Guide polynucleotide name	Target site description	Editor	Cas description	Target Site	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
GuideDesign90_ABE_NRN_20nt_3-9_021_+31946061_spCas9	TATA box	ABE_NRN_20nt_3-9_021	spCas9 NRN ABE	TTGTATA AAAGGCT GGGGGCT GG	3105	UUGUAUAA AAGGCUGG GGCC	3411	TGG
GuideDesign90_CBE_NRN_20nt_3-9_022_+31946061_spCas9	TATA box	CBE_NRN_20nt_3-9_022	spCas9 NRN CBE	TTGTATA AAAGGCT GGGGGCT GG	3106	UUGUAUAA AAGGCUGG GGCC	3412	TGG
GuideDesign90_MBE_NRN_20nt_3-9_023_+31946061_spCas9	TATA box	MBE_NRN_20nt_3-9_023	spCas9 NRN MBE	TTGTATA AAAGGCT GGGGGCT GG	3107	UUGUAUAA AAGGCUGG GGCC	3413	TGG
GuideDesign90_CBE_NRRH_20nt_3-9_031_+31946061_spCas9	TATA box	CBE_NRRH_20nt_3-9_031	spCas9 NRRH CBE	TTGTATA AAAGGCT GGGGGCT GGT	3108	UUGUAUAA AAGGCUGG GGCC	3414	TGGT
GuideDesign90_ABE_NGC_20nt_3-9_008_-31946048_spCas9	TATA box	ABE_NGC_20nt_3-9_008	spCas9 NGC ABE	TTTTATA CAATCTG TGTTCTG GC	3109	UUUUAUAC AAUCUGUG UUCU	3415	GGC
GuideDesign90_ABE_NGC_20nt_3-12_020_-31946048_spCas9	TATA box	ABE_NGC_20nt_3-12_020	spCas9 NGC IBE	TTTTATA CAATCTG TGTTCTG GC	3110	UUUUAUAC AAUCUGUG UUCU	3416	GGC
GuideDesign90_CBE_NGC_20nt_4-9_009_-31946048_spCas9	TATA box	CBE_NGC_20nt_4-9_009	spCas9 NGC CBE	TTTTATA CAATCTG TGTTCTG GC	3111	UUUUAUAC AAUCUGUG UUCU	3417	GGC
GuideDesign90_ABE_NG_20nt_3-9_027_-31946049_spCas9	TATA box	ABE_NG_20nt_3-9_027	spCas9 NG ABE	TTTTATA CAATCTG TGTTCTG G	3112	UUUUAUAC AAUCUGUG UUCU	3418	GG
GuideDesign90_CBE_NG_20nt_4-9_028_-31946049_spCas9	TATA box	CBE_NG_20nt_4-9_028	spCas9 NG CBE	TTTTATA CAATCTG TGTTCTG G	3113	UUUUAUAC AAUCUGUG UUCU	3419	GG

Guide polynucleotide name	Target site description	Editor	Cas description	Target Site	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
GuideDesign90_ABE_NRN_20nt_3-9_021_-31946048_spCas9	TATA box	ABE_NRN_20nt_3-9_021	spCas9 NRN ABE	TTTTATA CAATCTG TGTTC TGC	3114	UUUUAUAC AAUCUGUG UUCU	3420	GGC
GuideDesign90_CBE_NRN_20nt_3-9_022_-31946048_spCas9	TATA box	CBE_NRN_20nt_3-9_022	spCas9 NRN CBE	TTTTATA CAATCTG TGTTC TGC	3115	UUUUAUAC AAUCUGUG UUCU	3421	GGC
GuideDesign90_MBE_NRN_20nt_3-9_023_-31946048_spCas9	TATA box	MBE_NRN_20nt_3-9_023	spCas9 NRN MBE	TTTTATA CAATCTG TGTTC TGC	3116	UUUUAUAC AAUCUGUG UUCU	3422	GGC
GuideDesign90_ABE_NRCH_20nt_3-9_024_-31946047_spCas9	TATA box	ABE_NRCH_20nt_3-9_024	spCas9 NRCH ABE	TTTTATA CAATCTG TGTTC TGC A	3117	UUUUAUAC AAUCUGUG UUCU	3423	GGCA
GuideDesign90_CBE_NRCH_20nt_3-9_030_-31946047_spCas9	TATA box	CBE_NRCH_20nt_3-9_030	spCas9 NRCH CBE	TTTTATA CAATCTG TGTTC TGC A	3118	UUUUAUAC AAUCUGUG UUCU	3424	GGCA
GuideDesign90_ABE_NRN_20nt_3-9_021_+31946215_spCas9	Start codon	ABE_NRN_20nt_3-9_021	spCas9 NRN ABE	AACGCCA TGGGGAG CAATCTC AG	3119	AACGCCAU GGGGAGCA AUCU	3425	CAG
GuideDesign90_MBE_NRN_20nt_3-9_023_+31946215_spCas9	Start codon	MBE_NRN_20nt_3-9_023	spCas9 NRN MBE	AACGCCA TGGGGAG CAATCTC AG	3120	AACGCCAU GGGGAGCA AUCU	3426	CAG
GuideDesign90_ABE_NGC_20nt_3-9_008_+31946216_spCas9	Start codon	ABE_NGC_20nt_3-9_008	spCas9 NGC ABE	ACGCCAT GGGGAGC AATCTCA GC	3121	ACGCCAUG GGGAGCAA UCUC	3427	AGC
GuideDesign90_ABE_NGC_20nt_3-12_020_+31946216_spCas9	Start codon	ABE_NGC_20nt_3-12_020	spCas9 NGC IBE	ACGCCAT GGGGAGC AATCTCA GC	3122	ACGCCAUG GGGAGCAA UCUC	3428	AGC

Guide polynucleotide name	Target site description	Editor	Cas description	Target Site	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
GuideDesign90_ABE_NG_20nt_3-9_027_+31946216_spCas9	Start codon	ABE_NG_20nt_3-9_027	spCas9 NG ABE	ACGCCAT GGGGAGC AATCTCAG	3123	ACGCCAUG GGGAGCAA UCUC	3429	AG
GuideDesign90_ABE_NRN_20nt_3-9_021_+31946216_spCas9	Start codon	ABE_NRN_20nt_3-9_021	spCas9 NRN ABE	ACGCCAT GGGGAGC AATCTCAGC	3124	ACGCCAUG GGGAGCAA UCUC	3430	AGC
GuideDesign90_MBE_NRN_20nt_3-9_023_+31946216_spCas9	Start codon	MBE_NRN_20nt_3-9_023	spCas9 NRN MBE	ACGCCAT GGGGAGC AATCTCAGC	3125	ACGCCAUG GGGAGCAA UCUC	3431	AGC
GuideDesign90_ABE_NRCH_20nt_3-9_024_+31946216_spCas9	Start codon	ABE_NRCH_20nt_3-9_024	spCas9 NRCH ABE	ACGCCAT GGGGAGC AATCTCAGCC	3126	ACGCCAUG GGGAGCAA UCUC	3432	AGCC
GuideDesign90_CBE_NGA_20nt_3-16_035_-31946212_spCas9	Start codon	CBE_NGA_20nt_3-16_035	spCas9 IBE extended CBE	AGATTGC TCCCCAT GGCGTTGGA	3127	AGAUUGCU CCCCAUGG CGUU	3433	GGA
GuideDesign90_ABE_VTTN_22nt_5-9_017_+31946210_cas12b	Start codon	ABE_VTTN_22nt_5-9_017	cas12b ABE	CTTCCAA CGCCATG GGGAGCA ATCTC	3128	CAACGCCA UGGGGAGC AAUCUC	3434	CTTC
GuideDesign90_ABE_NG_20nt_3-9_027_-31946203_spCas9	Start codon	ABE_NG_20nt_3-9_027	spCas9 NG ABE	CCATGGC GTTGGAA GGCAGGAG	3129	CCAUGGCG UUGGAAGG CAGG	3435	AG
GuideDesign90_ABE_NRN_20nt_3-9_021_-31946202_spCas9	Start codon	ABE_NRN_20nt_3-9_021	spCas9 NRN ABE	CCATGGC GTTGGAA GGCAGGAGA	3130	CCAUGGCG UUGGAAGG CAGG	3436	AGA
GuideDesign90_MBE_NRN_20nt_3-9_023_-31946202_spCas9	Start codon	MBE_NRN_20nt_3-9_023	spCas9 NRN MBE	CCATGGC GTTGGAA GGCAGGAGA	3131	CCAUGGCG UUGGAAGG CAGG	3437	AGA

Guide polynucleotide name	Target site description	Editor	Cas description	Target Site	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
GuideDesign90_ABE_NGA_20nt_3-12_019_-31946202_sp_Cas9	Start codon	ABE_NGA_20nt_3-12_019	spCas9 VRQRI	CCATGGC GTTGGAA GGCAGGA GA	3132	CCAUGGCG UUGGAAGG CAGG	3438	AGA
GuideDesign90_ABE_NRN_20nt_3-9_021_-31946203_sp_Cas9	Start codon	ABE_NRN_20nt_3-9_021	spCas9 NRN ABE	CCCATGG CGTTGGA AGGCAGG AG	3133	CCCAUGGC GUUGGAAG GCAG	3439	GAG
GuideDesign90_CBE_NRN_20nt_3-9_022_-31946203_sp_Cas9	Start codon	CBE_NRN_20nt_3-9_022	spCas9 NRN CBE	CCCATGG CGTTGGA AGGCAGG AG	3134	CCCAUGGC GUUGGAAG GCAG	3440	GAG
GuideDesign90_MBE_NRN_20nt_3-9_023_-31946203_sp_Cas9	Start codon	MBE_NRN_20nt_3-9_023	spCas9 NRN MBE	CCCATGG CGTTGGA AGGCAGG AG	3135	CCCAUGGC GUUGGAAG GCAG	3441	GAG
GuideDesign90_CBE_NRRH_20nt_3-9_031_-31946202_sp_Cas9	Start codon	CBE_NRRH_20nt_3-9_031	spCas9 NRRH CBE	CCCATGG CGTTGGA AGGCAGG AGA	3136	CCCAUGGC GUUGGAAG GCAG	3442	GAGA
GuideDesign90_CBE_NGA_20nt_3-16_035_-31946204_sp_Cas9	Start codon	CBE_NGA_20nt_3-16_035	spCas9 IBE extended CBE	CCCCATG GCGTTGG AAGGCAG GA	3137	CCCCAUGG CGUUGGAA GGCA	3443	GGA
GuideDesign90_ABE_NG_20nt_3-9_027_-31946205_sp_Cas9	Start codon	ABE_NG_20nt_3-9_027	spCas9 NG ABE	CCCCATG GCGTTGG AAGGCAG G	3138	CCCCAUGG CGUUGGAA GGCA	3444	GG
GuideDesign90_CBE_NG_20nt_4-9_028_-31946205_sp_Cas9	Start codon	CBE_NG_20nt_4-9_028	spCas9 NG CBE	CCCCATG GCGTTGG AAGGCAG G	3139	CCCCAUGG CGUUGGAA GGCA	3445	GG
GuideDesign90_ABE_NRN_20nt_3-9_021_-	Start codon	ABE_NRN_20nt_3-9_021	spCas9 NRN ABE	CCCCATG GCGTTGG AAGGCAG GA	3140	CCCCAUGG CGUUGGAA GGCA	3446	GGA

Guide polynucleotide name	Target site description	Editor	Cas description	Target Site	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
_31946204_sp Cas9								
GuideDesign90_CBE_NRN_20nt_3-9_022 -_31946204_sp Cas9	Start codon	CBE_NRN_20nt_3-9_022	spCas9 NRN CBE	CCCCATG GCGTTGG AAGGCAG GA	3141	CCCCAUGG CGUUGGAA GGCA	3447	GGA
GuideDesign90_MBE_NRN_20nt_3-9_023 -_31946204_sp Cas9	Start codon	MBE_NRN_20nt_3-9_023	spCas9 NRN MBE	CCCCATG GCGTTGG AAGGCAG GA	3142	CCCCAUGG CGUUGGAA GGCA	3448	GGA
GuideDesign90_ABE_NGA_20nt_3-12_019 -_31946204_sp Cas9	Start codon	ABE_NGA_20nt_3-12_019	spCas9 VRQR IBE	CCCCATG GCGTTGG AAGGCAG GA	3143	CCCCAUGG CGUUGGAA GGCA	3449	GGA
GuideDesign90_CBE_NGA_20nt_4-9_006 -_31946204_sp Cas9	Start codon	CBE_NGA_20nt_4-9_006	spCas9 VRQR CBE	CCCCATG GCGTTGG AAGGCAG GA	3144	CCCCAUGG CGUUGGAA GGCA	3450	GGA
GuideDesign90_ABE_NRN_20nt_3-9_021 -_31946206_sp Cas9	Start codon	ABE_NRN_20nt_3-9_021	spCas9 NRN ABE	CTCCCCA TGGCGTT GGAAGGC AG	3145	CUCCCCAU GGCGUUGG AAGG	3451	CAG
GuideDesign90_CBE_NRN_20nt_3-9_022 -_31946206_sp Cas9	Start codon	CBE_NRN_20nt_3-9_022	spCas9 NRN CBE	CTCCCCA TGGCGTT GGAAGGC AG	3146	CUCCCCAU GGCGUUGG AAGG	3452	CAG
GuideDesign90_MBE_NRN_20nt_3-9_023 -_31946206_sp Cas9	Start codon	MBE_NRN_20nt_3-9_023	spCas9 NRN MBE	CTCCCCA TGGCGTT GGAAGGC AG	3147	CUCCCCAU GGCGUUGG AAGG	3453	CAG
GuideDesign90_ABE_VTTN_22nt_5-9_017 -_31946207_ca s12b	Start codon	ABE_VTTN_22nt_5-9_017	cas12b ABE	ATTGCTC CCCATGG CGTTGGA AGGCA	3148	CUCCCCAU GGCGUUGG AAGGCA	3454	ATTG

Guide polynucleotide name	Target site description	Editor	Cas description	Target Site	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
GuideDesign90_CBE_NGG_20nt_3-16_033_-31946213_SpCas9	Start codon	CBE_NGG_20nt_3-16_033	SpCas9 IBE CBE	GAGATTG CTCCCCA TGGCGTT GG	3149	GAGAUUGC UCCCCAUG GCGU	3455	TGG
GuideDesign90_ABE_NGG_20nt_3-9_002_-31946205_spCas9	Start codon	ABE_NGG_20nt_3-9_002	spCas9 ABE	TCCCCAT GGCGTTG GAAGGCA GG	3150	UCCCCAUG GCGUUGGA AGGC	3456	AGG
GuideDesign90_ABE_NG_20nt_3-9_027_-31946206_spCas9	Start codon	ABE_NG_20nt_3-9_027	spCas9 NG ABE	TCCCCAT GGCGTTG GAAGGCA G	3151	UCCCCAUG GCGUUGGA AGGC	3457	AG
GuideDesign90_CBE_NG_20nt_4-9_028_-31946206_spCas9	Start codon	CBE_NG_20nt_4-9_028	spCas9 NG CBE	TCCCCAT GGCGTTG GAAGGCA G	3152	UCCCCAUG GCGUUGGA AGGC	3458	AG
GuideDesign90_ABE_NGG_20nt_3-12_018_-31946205_spCas9	Start codon	ABE_NGG_20nt_3-12_018	spCas9 IBE	TCCCCAT GGCGTTG GAAGGCA GG	3153	UCCCCAUG GCGUUGGA AGGC	3459	AGG
GuideDesign90_ABE_NRN_20nt_3-9_021_-31946205_spCas9	Start codon	ABE_NRN_20nt_3-9_021	spCas9 NRN ABE	TCCCCAT GGCGTTG GAAGGCA GG	3154	UCCCCAUG GCGUUGGA AGGC	3460	AGG
GuideDesign90_CBE_NRN_20nt_3-9_022_-31946205_spCas9	Start codon	CBE_NRN_20nt_3-9_022	spCas9 NRN CBE	TCCCCAT GGCGTTG GAAGGCA GG	3155	UCCCCAUG GCGUUGGA AGGC	3461	AGG
GuideDesign90_MBE_NRN_20nt_3-9_023_-31946205_spCas9	Start codon	MBE_NRN_20nt_3-9_023	spCas9 NRN MBE	TCCCCAT GGCGTTG GAAGGCA GG	3156	UCCCCAUG GCGUUGGA AGGC	3462	AGG
GuideDesign90_CBE_NRRH_20nt_3-9_031_-	Start codon	CBE_NRRH_20nt_3-9_031	spCas9 NRRH CBE	TCCCCAT GGCGTTG GAAGGCA GGA	3157	UCCCCAUG GCGUUGGA AGGC	3463	AGGA

Guide polynucleotide name	Target site description	Editor	Cas description	Target Site	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
_31946204_sp Cas9								
GuideDesign90_CBE_NGG_20nt_4-9_003 -_31946205_sp Cas9	Start codon	CBE_NGG_20nt_4-9_003	spCas9 CBE	TCCCCAT GGCGTTG GAAGGCA GG	3158	UCCCCAUG GCGUUGGA AGGC	3464	AGG
GuideDesign90_CBE_NGG_20nt_3-9_029 -_31946205_sp Cas9	Start codon	CBE_NGG_20nt_3-9_029	spCas9 NGG CBE	TCCCCAT GGCGTTG GAAGGCA GG	3159	UCCCCAUG GCGUUGGA AGGC	3465	AGG
GuideDesign90_CBE_NGG_20nt_3-16_033 -_31946205_Sp Cas9	Start codon	CBE_NGG_20nt_3-16_033	SpCas9 IBE CBE	TCCCCAT GGCGTTG GAAGGCA GG	3160	UCCCCAUG GCGUUGGA AGGC	3466	AGG
GuideDesign90_ABE_NGC_20nt_3-12_020 -_31946208_sp Cas9	Start codon	ABE_NGC_20nt_3-12_020	spCas9 NGC IBE	TGCTCCC CATGGCG TTGGAAG GC	3161	UGCUCUCCC AUGGCGUU GGAA	3467	GGC
GuideDesign90_CBE_NGC_20nt_4-9_009 -_31946208_sp Cas9	Start codon	CBE_NGC_20nt_4-9_009	spCas9 NGC CBE	TGCTCCC CATGGCG TTGGAAG GC	3162	UGCUCUCCC AUGGCGUU GGAA	3468	GGC
GuideDesign90_ABE_NG_20nt_3-9_027 -_31946209_sp Cas9	Start codon	ABE_NG_20nt_3-9_027	spCas9 NG ABE	TGCTCCC CATGGCG TTGGAAG G	3163	UGCUCUCCC AUGGCGUU GGAA	3469	GG
GuideDesign90_CBE_NG_20nt_4-9_028 -_31946209_sp Cas9	Start codon	CBE_NG_20nt_4-9_028	spCas9 NG CBE	TGCTCCC CATGGCG TTGGAAG G	3164	UGCUCUCCC AUGGCGUU GGAA	3470	GG
GuideDesign90_ABE_NRN_20nt_3-9_021 -_31946208_sp Cas9	Start codon	ABE_NRN_20nt_3-9_021	spCas9 NRN ABE	TGCTCCC CATGGCG TTGGAAG GC	3165	UGCUCUCCC AUGGCGUU GGAA	3471	GGC

Guide polynucleotide name	Target site description	Editor	Cas description	Target Site	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
GuideDesign90_CBE_NRN_20nt_3-9_022_-31946208_sp_Cas9	Start codon	CBE_NRN_20nt_3-9_022	spCas9 NRN CBE	TGCTCCC CATGGCG TTGGAAG GC	3166	UGCUCCCC AUGGCGUU GGAA	3472	GGC
GuideDesign90_MBE_NRN_20nt_3-9_023_-31946208_sp_Cas9	Start codon	MBE_NRN_20nt_3-9_023	spCas9 NRN MBE	TGCTCCC CATGGCG TTGGAAG GC	3167	UGCUCCCC AUGGCGUU GGAA	3473	GGC
GuideDesign90_ABE_NRH_20nt_3-9_024_-31946207_sp_Cas9	Start codon	ABE_NRH_20nt_3-9_024	spCas9 NRH ABE	TGCTCCC CATGGCG TTGGAAG GCA	3168	UGCUCCCC AUGGCGUU GGAA	3474	GGCA
GuideDesign90_CBE_NRH_20nt_3-9_030_-31946207_sp_Cas9	Start codon	CBE_NRH_20nt_3-9_030	spCas9 NRH CBE	TGCTCCC CATGGCG TTGGAAG GCA	3169	UGCUCCCC AUGGCGUU GGAA	3475	GGCA
GuideDesign90_CBE_NG_20nt_4-9_028_-31946210_sp_Cas9	Start codon	CBE_NG_20nt_4-9_028	spCas9 NG CBE	TTGCTCC CCATGGC GTTGGAA G	3170	UUGCUCCC CAUGGCGU UGGA	3476	AG
GuideDesign90_CBE_NRN_20nt_3-9_022_-31946209_sp_Cas9	Start codon	CBE_NRN_20nt_3-9_022	spCas9 NRN CBE	TTGCTCC CCATGGC GTTGGAA GG	3171	UUGCUCCC CAUGGCGU UGGA	3477	AGG
GuideDesign90_MBE_NRN_20nt_3-9_023_-31946209_sp_Cas9	Start codon	MBE_NRN_20nt_3-9_023	spCas9 NRN MBE	TTGCTCC CCATGGC GTTGGAA GG	3172	UUGCUCCC CAUGGCGU UGGA	3478	AGG
GuideDesign90_CBE_NRRH_20nt_3-9_031_-31946208_sp_Cas9	Start codon	CBE_NRRH_20nt_3-9_031	spCas9 NRRH CBE	TTGCTCC CCATGGC GTTGGAA GGC	3173	UUGCUCCC CAUGGCGU UGGA	3479	AGGC
GuideDesign90_CBE_NGG_20nt_4-9_003	Start codon	CBE_NGG_20nt_4-9_003	spCas9 CBE	TTGCTCC CCATGGC	3174	UUGCUCCC CAUGGCGU UGGA	3480	AGG

Guide polynucleotide name	Target site description	Editor	Cas description	Target Site	SEQ ID NO	Spacer sequence	SEQ ID NO	PAM sequence
9_003_- _31946209_sp Cas9				GTTGGAA GG				
GuideDesign9 0_CBE_NGG_ 20nt_3- 9_029_- _31946209_sp Cas9	Start codon	CBE_NGG _20nt_3- 9_029	spCas9 NGG CBE	TTGCTCC CCATGGC GTTGGAA GG	3175	UUGCUC CAUGGCGU UGGA	3481	AGG
GuideDesign9 0_CBE_NGG_ 20nt_3- 16_033_- _31946209_Sp Cas9	Start codon	CBE_NGG _20nt_3- 16_033	SpCas9 IBE CBE	TTGCTCC CCATGGC GTTGGAA GG	3176	UUGCUC CAUGGCGU UGGA	3482	AGG

Table 2E. Representative spacer and target site sequences relating to altering a TATA box or start codon of a complement factor B polynucleotide using base editing.

Guide polynucleotide name	Target site name	Target site description	Editor	Cas9 variant
gRNA3642	TSBTx6496	CFB_TATA_locus	ABE_NGG_20nt_3- 9_002	spCas9 ABE
gRNA3643	TSBTx6497	CFB_TATA_locus	ABE_NGG_20nt_3- 9_002	spCas9 ABE
gRNA3644	TSBTx6498	CFB_TATA_locus	ABE_NGG_20nt_3- 9_002	spCas9 ABE
gRNA3645	TSBTx6499	CFB_TATA_locus	ABE_NGG_20nt_3- 9_002	spCas9 ABE
gRNA3646	TSBTx6500	CFB_TATA_locus	ABE_NGG_20nt_3- 9_002	spCas9 ABE
gRNA3647	TSBTx6501	CFB_TATA_locus	ABE_NGG_20nt_3- 9_002	spCas9 ABE
gRNA3648	TSBTx6502	CFB_TATA_locus	ABE_NGG_20nt_3- 9_002	spCas9 ABE
gRNA3649	TSBTx6503	CFB_TATA_locus	ABE_NGG_20nt_3- 9_002	spCas9 ABE
gRNA3650	TSBTx6504	CFB_TATA_locus	ABE_NGG_20nt_3- 9_002	spCas9 ABE
gRNA3651	TSBTx6505	CFB_TATA_locus	ABE_NGG_20nt_3- 9_002	spCas9 ABE
gRNA3652	TSBTx6506	CFB_TATA_locus	ABE_NGA_20nt_3- 9_005	spCas9 VRQR ABE
gRNA3653	TSBTx6507	CFB_TATA_locus	ABE_NGC_20nt_3- 9_008	spCas9 NGC ABE
gRNA3654	TSBTx6508	CFB_TATA_locus	ABE_NGC_20nt_3- 9_008	spCas9 NGC ABE

Guide polynucleotide name	Target site name	Target site description	Editor	Cas9 variant
gRNA3655	TSBTx6509	CFB_TATA_locus	ABE_NNNRRT_21nt_5-14_014	saCas9 KKH ABE
gRNA3656	TSBTx6510	CFB_TATA_locus	ABE_NNNRRT_21nt_5-14_014	saCas9 KKH ABE
gRNA3657	TSBTx6511	Start codon	ABE_NGC_20nt_3-9_008	spCas9 NGC ABE
gRNA3658	TSBTx6512	Start codon	ABE_NGG_20nt_3-12_018	spCas9 IBE
gRNA3659	TSBTx6513	Start codon	ABE_NGG_20nt_13-16_032	SpCas9 IBE_expanded ABE
gRNA3660	TSBTx6514	Start codon	ABE_NGA_20nt_3-9_005	spCas9 VRQR ABE
gRNA3661	TSBTx6515	Start codon	ABE_NGA_20nt_3-9_005	spCas9 VRQR ABE
gRNA3662	TSBTx6516	Start codon	ABE_NGA_20nt_3-12_034	SpCas9 IBE expanded ABE

Table 2E (CONTINUED).

Guide polynucleotide name	Target sequence	SEQ ID NO	PAM sequence	Spacer sequence	SEQ ID NO
gRNA3642	CAGAACACAGATTGTATAAAAGG	3483	NGG	CAGAACACAGAUUGUAUAAA	3504
gRNA3643	ACACAGATTGTATAAAAGGCTG	3484	NGG	ACACAGAUUGUAUAAAAAGGC	3505
gRNA3644	CACAGATTGTATAAAAGGCTGG	3485	NGG	CACAGAUUGUAUAAAAGG	3506
gRNA3645	ACAGATTGTATAAAAGGCTGGG	3486	NGG	ACAGAUUGUAUAAAAGG	3507
gRNA3646	CAGATTGTATAAAAGGCTGGGG	3487	NGG	CAGAUUGUAUAAAAGGC	3508
gRNA3647	TATAAAAGGCTGGGGGCTGGTG	3488	NGG	UAUAAAAGGCUGGGGGC	3509
gRNA3648	ATAAAAGGCTGGGGGCTGGTGG	3489	NGG	AUAAAAGGCUGGGGGCU	3510
gRNA3649	TAAAAGGCTGGGGGCTGGTGGG	3490	NGG	UAAAAGGCUGGGGGCUG	3511
gRNA3650	CTTTTATACAATCTGTGTTCTG	3491	NGG	CUUUUAUACAAUCUGUG	3512
gRNA3651	AATCTGTGTTCTGGCACCTGCG	3492	NGG	AAUCUGUGUUCUGGCAC	3513
gRNA3652	AAAAGGCTGGGGGCTGGTGGG	3493	NGA	AAAAGGCUGGGGGCUGG	3514
gRNA3653	AGAACACAGATTGTATAAAAGG	3494	NGC	AGAACACAGAUUGUAUA	3515
gRNA3654	ATCTGTGTTCTGGCACCTGCGG	3495	NGC	AUCUGUGUUCUGGCACC	3516

Guide polynucleotide name	Target sequence	SEQ ID NO	PAM sequence	Spacer sequence	SEQ ID NO
gRNA3655	AGATTGTATAAAAGGCTGGGGCTGGT	3496	NNNRR T	AGAUUGUAUAAAAGGCU GGGG	3517
gRNA3656	CCACCAGCCCCCAGCCTTTTATACAAT	3497	NNNRR T	CCACCAGCCCCCAGCCU UUUA	3518
gRNA3657	TGCTCCCCATGGCGTTGGAAGG C	3498	NGC	UGCUCUCCCAUGGCGUUG GAA	3519
gRNA3658	TTGCTCCCCATGGCGTTGGAAG G	3499	NGG	UUGCUCUCCCAUGGCGUU GGA	3520
gRNA3659	GAGATTGCTCCCCATGGCGTTG G	3500	NGG	GAGAUUGCUCUCCCAUGG CGU	3521
gRNA3660	CCCCATGGCGTTGGAAGGCAGG A	3501	NGA	CCCCAUGGCGUUGGAAG GCA	3522
gRNA3661	CCATGGCGTTGGAAGGCAGGAG A	3502	NGA	CCAUGGCGUUGGAAGGC AGG	3523
gRNA3662	AGATTGCTCCCCATGGCGTTGG A	3503	NGA	AGAUUGCUCUCCCAUGGC GUU	3524

Table 2F. Representative spacer and target site sequences relating to disruption of a complement factor B splice site using base editing.

Guide Polynucleotide Name	Target Site Name	Spacer Sequence	SEQ ID NO	Target Sequence (PAM is underlined and target nucleotide is in bold text)	SEQ ID NO	Cyno Cross (X) Reactivity	Target Site Location Description
gRNA1193	TSBT x3826	CCUCAGAU GUCUAUGU GUUU	3525	CCTC <u>AGATGTCT</u> ATGTGTTTGGG	3529	Y	Exon 10-5'
gRNA1202	TSBT x3835	UCUCACCU CUGCAAGU AUUG	3526	TCTC <u>ACCTCTGC</u> AAGTATTGGGG	3530	Y	Exon 16-3'
gRNA1204	TSBT x3837	GCUUACAA UGACUGAG AUCU	3527	GCTT <u>ACAATGAC</u> TGAGATCTTGG	3792	N	Exon 11-3'
gRNA2067	TSBT x3837	UGC UUACA AUGACUGA GAUCU	3528	TGCTT <u>ACAATGA</u> CTGAGATCTTGG	3793	N	Exon 11-3'

- 5 sg23/sgRNA_088 spacer sequence: CAGGAUCCGCACAGACUCCA (SEQ ID NO: 3794) (target gene: ALAS1). The target sequence corresponding to sg23 is as follows, where the PAM sequence is in **bold**: CAGGATCCGCACAGACTCCAGGG (SEQ ID NO: 3795). crRNA2/gRNA2002 spacer sequence: UCCCCGUUCUGAAGUCGUG (SEQ ID NO: 3796). Target site corresponding to crRNA2 (TSBTx4946): TCCCCGTTCTCGAAGTCGTG**TGG** (SEQ ID NO: 3797), where the PAM sequence is in bold.
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NUCLEOBASE EDITORS

Useful in the methods and compositions described herein are nucleobase editors that edit, modify or alter a target nucleotide sequence of a polynucleotide. Nucleobase editors described herein typically include a polynucleotide programmable nucleotide binding domain and a nucleobase editing domain (*e.g.*, adenosine deaminase, cytidine deaminase, or a dual deaminase). A polynucleotide programmable nucleotide binding domain, when in conjunction with a bound guide polynucleotide (*e.g.*, gRNA), can specifically bind to a target polynucleotide sequence and thereby localize the base editor to the target nucleic acid sequence desired to be edited.

Polynucleotide Programmable Nucleotide Binding Domain

Polynucleotide programmable nucleotide binding domains bind polynucleotides (*e.g.*, RNA, DNA). A polynucleotide programmable nucleotide binding domain of a base editor can itself comprise one or more domains (*e.g.*, one or more nuclease domains). In some embodiments, the nuclease domain of a polynucleotide programmable nucleotide binding domain comprises an endonuclease or an exonuclease.

Disclosed herein are base editors comprising a polynucleotide programmable nucleotide binding domain comprising all or a portion (*e.g.*, a functional portion) of a CRISPR protein (*i.e.*, a base editor comprising as a domain all or a portion (*e.g.*, a functional portion) of a CRISPR protein (*e.g.*, a Cas protein), also referred to as a “CRISPR protein-derived domain” of the base editor). A CRISPR protein-derived domain incorporated into a base editor can be modified compared to a wild-type or natural version of the CRISPR protein. A CRISPR protein-derived domain can comprise one or more mutations, insertions, deletions, rearrangements and/or recombinations relative to a wild-type or natural version of the CRISPR protein.

Cas proteins that can be used herein include class 1 and class 2. Non-limiting examples of Cas proteins include Cas1, Cas1B, Cas2, Cas3, Cas4, Cas5, Cas5d, Cas5t, Cas5h, Cas5a, Cas6, Cas7, Cas8, Cas9 (also known as Csn1 or Csx12), Cas10, Csy1, Csy2, Csy3, Csy4, Cse1, Cse2, Cse3, Cse4, Cse5e, Csc1, Csc2, Csa5, Csn1, Csn2, Csm1, Csm2, Csm3, Csm4, Csm5, Csm6, Cmr1, Cmr3, Cmr4, Cmr5, Cmr6, Csb1, Csb2, Csb3, Csx17, Csx14, Csx10, Csx16, CsaX, Csx3, Csx1, Csx1S, Csf1, Csf2, CsO, Csf4, Csd1, Csd2, Cst1, Cst2, Csh1, Csh2, Csa1, Csa2, Csa3, Csa4, Csa5, Cas12a/Cpf1, Cas12b/C2c1 (*e.g.*, SEQ ID NO: 232), Cas12c/C2c3, Cas12d/CasY, Cas12e/CasX, Cas12g, Cas12h, Cas12i, and Cas12j/CasΦ, CARF, DinG, Turbo Cas9 (*i.e.*, an SpCas9 with the amino acid alterations

Q844R, V842L, F846Y, L847M, and I852F), homologues thereof, or modified versions thereof. A CRISPR enzyme can direct cleavage of one or both strands at a target sequence, such as within a target sequence and/or within a complement of a target sequence. For example, a CRISPR enzyme can direct cleavage of one or both strands within about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 50, 100, 200, 500, or more base pairs from the first or last nucleotide of a target sequence.

A vector that encodes a CRISPR enzyme that is mutated to with respect to a corresponding wild-type enzyme such that the mutated CRISPR enzyme lacks the ability to cleave one or both strands of a target polynucleotide containing a target sequence can be used. A Cas protein (e.g., Cas9, Cas12) or a Cas domain (e.g., Cas9, Cas12) can refer to a polypeptide or domain with at least or at least about 50%, 60%, 70%, 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity and/or sequence homology to a wild-type exemplary Cas polypeptide or Cas domain. Cas (e.g., Cas9, Cas12) can refer to the wild-type or a modified form of the Cas protein that can comprise an amino acid change such as a deletion, insertion, substitution, variant, mutation, fusion, chimera, or any combination thereof.

In some embodiments, a CRISPR protein-derived domain of a base editor can include all or a portion (e.g., a functional portion) of Cas9 from *Corynebacterium ulcerans* (NCBI Refs: NC_015683.1, NC_017317.1); *Corynebacterium diphtheria* (NCBI Refs: NC_016782.1, NC_016786.1); *Spiroplasma syrophidicola* (NCBI Ref: NC_021284.1); *Prevotella intermedia* (NCBI Ref: NC_017861.1); *Spiroplasma taiwanense* (NCBI Ref: NC_021846.1); *Streptococcus iniae* (NCBI Ref: NC_021314.1); *Belliella baltica* (NCBI Ref: NC_018010.1); *Psychroflexus torquis* (NCBI Ref: NC_018721.1); *Streptococcus thermophilus* (NCBI Ref: YP_820832.1); *Listeria innocua* (NCBI Ref: NP_472073.1); *Campylobacter jejuni* (NCBI Ref: YP_002344900.1); *Neisseria meningitidis* (NCBI Ref: YP_002342100.1), *Streptococcus pyogenes*, or *Staphylococcus aureus*.

Some aspects of the disclosure provide high fidelity Cas9 domains. High fidelity Cas9 domains are known in the art and described, for example, in Kleinstiver, B.P., *et al.* "High-fidelity CRISPR-Cas9 nucleases with no detectable genome-wide off-target effects." *Nature* 529, 490-495 (2016); and Slaymaker, I.M., *et al.* "Rationally engineered Cas9 nucleases with improved specificity." *Science* 351, 84-88 (2015); the entire contents of each of which are incorporated herein by reference. An Exemplary high fidelity Cas9 domain is provided in the Sequence Listing as SEQ ID NO: 233.

In some embodiments, any of the Cas9 fusion proteins or complexes provided herein comprise one or more of a D10A, N497X, a R661X, a Q695X, and/or a Q926X mutation, or a corresponding mutation in any of the amino acid sequences provided herein, wherein X is any amino acid. .

5 Typically, Cas9 proteins, such as Cas9 from *S. pyogenes* (spCas9), require a “protospacer adjacent motif (PAM)” or PAM-like motif, which is a 2-6 base pair DNA sequence immediately following the DNA sequence targeted by the Cas9 nuclease in the CRISPR bacterial adaptive immune system. The presence of an NGG PAM sequence is required to bind a particular nucleic acid region, where the “N” in “NGG” is adenosine (A),
10 thymidine (T), or cytosine (C), and the G is guanosine. In some embodiments, any of the fusion proteins or complexes provided herein may contain a Cas9 domain that is capable of binding a nucleotide sequence that does not contain a canonical (*e.g.*, NGG) PAM sequence. Cas9 domains that bind to non-canonical PAM sequences have been described in the art and would be apparent to the skilled artisan. For example, Cas9 domains that bind non-canonical
15 PAM sequences have been described in Kleinstiver, B. P., *et al.*, “Engineered CRISPR-Cas9 nucleases with altered PAM specificities” *Nature* 523, 481-485 (2015); and Kleinstiver, B. P., *et al.*, “Broadening the targeting range of *Staphylococcus aureus* CRISPR-Cas9 by modifying PAM recognition” *Nature Biotechnology* 33, 1293-1298 (2015); the entire contents of each are hereby incorporated by reference.

20 In some embodiments, the napDNAbp is a circular permutant (*e.g.*, SEQ ID NO: 238).

In some embodiments, the polynucleotide programmable nucleotide binding domain comprises a nickase domain. Herein the term “nickase” refers to a polynucleotide programmable nucleotide binding domain comprising a nuclease domain that is capable of
25 cleaving only one strand of the two strands in a duplexed nucleic acid molecule (*e.g.*, DNA). For example, where a polynucleotide programmable nucleotide binding domain comprises a nickase domain derived from Cas9, the Cas9-derived nickase domain can include a D10A mutation and a histidine at position 840. In another example, a Cas9-derived nickase domain comprises an H840A mutation, while the amino acid residue at position 10 remains a D.

30 In some embodiments, a Cas9 nuclease has an inactive (*e.g.*, an inactivated) DNA cleavage domain, that is, the Cas9 is a nickase, referred to as an “nCas9” protein (for “nickase” Cas9; SEQ ID No: 201). The Cas9 nickase may be a Cas9 protein that is capable of cleaving only one strand of a duplexed nucleic acid molecule (*e.g.*, a duplexed DNA

molecule). In some embodiments the Cas9 nickase comprises an amino acid sequence that is at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 99.5% identical to any one of the Cas9 nickases provided herein. Additional suitable Cas9 nickases will be apparent to those of skill in the art based on this disclosure and knowledge in the field and are within the scope of this disclosure.

Also provided herein are base editors comprising a polynucleotide programmable nucleotide binding domain which is catalytically dead (*i.e.*, incapable of cleaving a target polynucleotide sequence). For example, in the case of a base editor comprising a Cas9 domain, the Cas9 can comprise both a D10A mutation and an H840A mutation. In further embodiments, a catalytically dead polynucleotide programmable nucleotide binding domain comprises a point mutation (*e.g.*, D10A or H840A) as well as a deletion of all or a portion (*e.g.*, a functional portion) of a nuclease domain. dCas9 domains are known in the art and described, for example, in Qi *et al.*, “Repurposing CRISPR as an RNA-guided platform for sequence-specific control of gene expression.” *Cell*. 2013; 152(5):1173-83, the entire contents of which are incorporated herein by reference.

The term “protospacer adjacent motif (PAM)” or PAM-like motif refers to a 2-6 base pair DNA sequence immediately following the DNA sequence targeted by a nucleic acid programmable DNA binding protein. In some embodiments, the PAM can be a 5' PAM (*i.e.*, located upstream of the 5' end of the protospacer). In other embodiments, the PAM can be a 3' PAM (*i.e.*, located downstream of the 5' end of the protospacer). The PAM sequence can be any PAM sequence known in the art. Suitable PAM sequences include, but are not limited to, NGG, NGA, NGC, NGN, NGT, NGTT, NGCG, NGAG, NGAN, NGNG, NGCN, NGCG, NGTN, NNGRRT, NNNRRT, NNGRR(N), TTTV, TYCV, TYCV, TATV, NNNNGATT, NNAGAAW, or NAAAAC. Y is a pyrimidine; N is any nucleotide base; W is A or T.

A base editor provided herein can comprise a CRISPR protein-derived domain that is capable of binding a nucleotide sequence that contains a canonical or non-canonical protospacer adjacent motif (PAM) sequence.

In some embodiments, the PAM is an “NRN” PAM where the “N” in “NRN” is adenine (A), thymine (T), guanine (G), or cytosine (C), and the R is adenine (A) or guanine (G); or the PAM is an “NYN” PAM, wherein the “N” in NYN is adenine (A), thymine (T), guanine (G), or cytosine (C), and the Y is cytidine (C) or thymine (T), for example, as

described in R.T. Walton *et al.*, 2020, *Science*, 10.1126/science.aba8853 (2020), the entire contents of which are incorporated herein by reference.

Several PAM variants are described in **Table 3** below.

5 **Table 3. Cas9 proteins and corresponding PAM sequences. N is A, C, T, or G; and V is A, C, or G.**

Variant	PAM
spCas9	NGG
spCas9-VRQR	NGA
spCas9-VRER	NGCG
xCas9 (sp)	NGN
saCas9	NNGRRT
saCas9-KKH	NNNRRT
spCas9-MQKSER	NGCG
spCas9-MQKSER	NGCN
spCas9-LRKIQK	NGTN
spCas9-LRVSQK	NGTN
spCas9-LRVSQL	NGTN
spCas9-MQKFRAER	NGC
Cpf1	5' (TTTV)
SpyMac	5' -NAA-3'

In some embodiments, the PAM is NGC. In some embodiments, the NGC PAM is recognized by a Cas9 variant. In some embodiments, the NGC PAM Cas9 variant includes
10 one or more amino acid substitutions selected from D1135M, S1136Q, G1218K, E1219F, A1322R, D1332A, R1335E, and T1337R (collectively termed “MQKFRAER”) of spCas9 (SEQ ID No: 197), or a corresponding mutation in another Cas9. In some embodiments, the Cas9 variant contains one or more amino acid substitutions selected from D1135V, G1218R, R1335Q, and T1337R (collectively termed VRQR) of spCas9 (SEQ ID No: 197), or a
15 corresponding mutation in another Cas9. In some embodiments, the Cas9 variant contains one or more amino acid substitutions selected from D1135V, G1218R, R1335E, and T1337R (collectively termed VRER) of spCas9 (SEQ ID No: 197), or a corresponding mutation in another Cas9. In some embodiments, the Cas9 variant contains one or more amino acid

substitutions selected from E782K, N968K, and R1015H (collectively termed KHH) of saCas9 (SEQ ID NO: 218). In some embodiments, the Cas9 variant includes one or more amino acid substitutions selected from D1135M, S1136Q, G1218K, E1219S, R1335E, and T1337R (collectively termed “MQKSER”) of spCas9 (SEQ ID No: 197), or a corresponding mutation in another Cas9.

In some cases, a Cas9 variant has specificity for the PAM 5' -NGC-3'. In some embodiments, a Cas9 variant includes one or more amino acid substitutions selected from D1135M, S1136Q, G1218K, E1219F, A1322R, D1332A, R1335E, and T1337K of spCas9 (SEQ ID No: 197), or a corresponding mutation in another Cas9. In some embodiments, a Cas9 variant includes one or more amino acid substitutions selected from D1135M, S1136Y, G1218K, E1219F, A1322R, D1332A, R1335E, and T1337K of spCas9 (SEQ ID No: 197), or a corresponding mutation in another Cas9. In some embodiments, the a Cas9 variant includes one or more amino acid substitutions selected from D1135L, S1136Y, G1218K, E1219F, A1322R, D1332A, R1335E, and T1337R of spCas9 (SEQ ID No: 197), or a corresponding mutation in another Cas9. In some embodiments, a Cas9 variant includes one or more amino acid substitutions selected from D1135M, S1136Y, G1218K, E1219F, A1322R, D1332A, R1335E, and T1337K of spCas9 (SEQ ID No: 197), or a corresponding mutation in another Cas9. In some embodiments, a Cas9 variant includes one or more amino acid substitutions selected from D1135L, S1136Y, G1218K, E1219F, A1283D, A1322R, D1332A, R1335E, and T1337K of spCas9 (SEQ ID No: 197), or a corresponding mutation in another Cas9. In some embodiments, a Cas9 variant includes one or more amino acid substitutions selected from A61R, L1111R, D1135L, S1136W, G1218K, E1219Q, N1317R, A1322R, R1333P, R1335Q, and T1337R of spCas9 (SEQ ID No: 197) (SpRY), or a corresponding mutation in another Cas9. In some embodiments, a Cas9 variant includes one or more amino acid substitutions selected from D1135L, S1136Q, G1218K, E1219F, E1250K, A1283D, A1322R, D1332A, R1335E, and T1337K of spCas9 (SEQ ID No: 197), or a corresponding mutation in another Cas9. In some embodiments, a Cas9 variant includes one or more amino acid substitutions selected from D1135M, S1136Y, G1218K, E1219F, E1250K, A1283D, A1322R, D1332A, R1335E, and T1337R of spCas9 (SEQ ID No: 197), or a corresponding mutation in another Cas9. In some embodiments, a Cas9 variant includes one or more amino acid substitutions selected from R765A, Q768A, D1135L, S1136Y, G1218K, A1283D, E1219F, A1322R, D1332A, R1335E, and T1337K of spCas9 (SEQ ID No: 197), or a corresponding mutation in another Cas9. In some embodiments, any of the Cas9 proteins

provided herein, including an SpCas9 comprises any one, two, three, four, five, six, seven, eight, nine, or ten of the following amino acid substitutions in a corresponding residue:

R765A, Q768A, W1126R, R1359W, E1250K, A1239T, A1239V, A1283D, R1335D, D1135L, D1135M, D1135R, D1135W, S1136H, S1136Q, S1136Y, G1218D, G1218K,
 5 G1218R, G1218E, G1218L, E1219F, E1219K, E1219N, A1322A, A1322R, A1322K, D1332A, R1335V, T1337K, T1337T, D1332A, D1135V and T1337R.

In some embodiments, a CRISPR protein-derived domain of a base editor comprises all or a portion (e.g., a functional portion) of a Cas9 protein with a canonical PAM sequence (NGG). In other embodiments, a Cas9-derived domain of a base editor can employ a non-
 10 canonical PAM sequence. Such sequences have been described in the art and would be apparent to the skilled artisan. For example, Cas9 domains that bind non-canonical PAM sequences have been described in Kleinstiver, B. P., *et al.*, “Engineered CRISPR-Cas9 nucleases with altered PAM specificities” *Nature* 523, 481-485 (2015); and Kleinstiver, B. P., *et al.*, “Broadening the targeting range of *Staphylococcus aureus* CRISPR-Cas9 by modifying
 15 PAM recognition” *Nature Biotechnology* 33, 1293-1298 (2015); R.T. Walton *et al.* “Unconstrained genome targeting with near-PAMless engineered CRISPR-Cas9 variants” *Science* 10.1126/science.aba8853 (2020); Hu *et al.* “Evolved Cas9 variants with broad PAM compatibility and high DNA specificity,” *Nature*, 2018 Apr. 5, 556(7699), 57-63; Miller *et al.*, “Continuous evolution of SpCas9 variants compatible with non-G PAMs” *Nat. Biotechnol.*, 2020 Apr;38(4):471-481; the entire contents of each are hereby incorporated by
 20 reference.

Fusion Proteins or Complexes Comprising a NapDNAbp and a Cytidine Deaminase and/or Adenosine Deaminase

Some aspects of the disclosure provide fusion proteins or complexes comprising a
 25 Cas9 domain or other nucleic acid programmable DNA binding protein (e.g., Cas12) and one or more cytidine deaminase, adenosine deaminase, or cytidine adenosine deaminase domains. It should be appreciated that the Cas9 domain may be any of the Cas9 domains or Cas9 proteins (e.g., dCas9 or nCas9) provided herein. In some embodiments, any of the Cas9
 30 domains or Cas9 proteins (e.g., dCas9 or nCas9) provided herein may be fused with any of the cytidine deaminases and/or adenosine deaminases provided herein. The domains of the base editors disclosed herein can be arranged in any order.

In some embodiments, the fusion proteins or complexes comprising a cytidine deaminase or adenosine deaminase and a napDNAbp (e.g., Cas9 or Cas12 domain) do not

include a linker sequence. In some embodiments, a linker is present between the cytidine or adenosine deaminase and the napDNAbp. In some embodiments, cytidine or adenosine deaminase and the napDNAbp are fused via any of the linkers provided herein. For example, in some embodiments the cytidine or adenosine deaminase and the napDNAbp are fused via
5 any of the linkers provided herein.

It should be appreciated that the fusion proteins or complexes of the present disclosure may comprise one or more additional features. For example, in some embodiments, the fusion protein or complex may comprise inhibitors, cytoplasmic localization sequences, export sequences, such as nuclear export sequences, or other
10 localization sequences, as well as sequence tags that are useful for solubilization, purification, or detection of the fusion proteins or complexes. Suitable protein tags provided herein include, but are not limited to, biotin carboxylase carrier protein (BCCP) tags, myc-tags, calmodulin-tags, FLAG-tags, hemagglutinin (HA)-tags, polyhistidine tags, also referred to as histidine tags or His-tags, maltose binding protein (MBP)-tags, nus-tags, glutathione-S-
15 transferase (GST)-tags, green fluorescent protein (GFP)-tags, thioredoxin-tags, S-tags, Softags (*e.g.*, Softag 1, Softag 3), strep-tags, biotin ligase tags, FLAsH tags, V5 tags, and SBP-tags. Additional suitable sequences will be apparent to those of skill in the art. In some embodiments, the fusion protein or complex comprises one or more His tags.

Exemplary, yet nonlimiting, fusion proteins are described in International PCT
20 Application Nos. PCT/US2017/045381, PCT/US2019/044935, and PCT/US2020/016288, each of which is incorporated herein by reference for its entirety.

Fusion Proteins or Complexes with Internal Insertions

Provided herein are fusion proteins or complexes comprising a heterologous
25 polypeptide fused to a nucleic acid programmable nucleic acid binding protein, for example, a napDNAbp. The heterologous polypeptide can be fused to the napDNAbp at a C-terminal end of the napDNAbp, an N-terminal end of the napDNAbp, or inserted at an internal location of the napDNAbp. In some embodiments, the heterologous polypeptide is a deaminase (*e.g.*, cytidine or adenosine deaminase) or a functional fragment thereof. For
30 example, a fusion protein can comprise a deaminase flanked by an N- terminal fragment and a C-terminal fragment of a Cas9 or Cas12 (*e.g.*, Cas12b/C2c1), polypeptide.

The deaminase can be a circular permutant deaminase. In some embodiments, the deaminase is a circular permutant TadA, circularly permuted at amino acid residue 116, 136, or 65 as numbered in a TadA reference sequence.

The fusion protein or complexes can comprise more than one deaminase. The fusion protein or complex can comprise, for example, 1, 2, 3, 4, 5 or more deaminases. The deaminases in a fusion protein or complex can be adenosine deaminases, cytidine deaminases, or a combination thereof.

- 5 In some embodiments, the napDNAbp in the fusion protein or complex contains a Cas9 polypeptide or a fragment thereof. The Cas9 polypeptide can be a variant Cas9 polypeptide. The Cas9 polypeptide can be a circularly permuted Cas9 protein.

- The heterologous polypeptide (*e.g.*, deaminase) can be inserted in the napDNAbp (*e.g.*, Cas9 or Cas12 (*e.g.*, Cas12b/C2c1)) at a suitable location, for example, such that the
 10 napDNAbp retains its ability to bind the target polynucleotide and a guide nucleic acid. A deaminase (*e.g.*, adenosine deaminase, cytidine deaminase, or adenosine deaminase and cytidine deaminase (dual deaminase)) can be inserted into a napDNAbp without compromising function of the deaminase (*e.g.*, base editing activity) or the napDNAbp (*e.g.*, ability to bind to target nucleic acid and guide nucleic acid).

- 15 In some embodiments, the deaminase (*e.g.*, adenosine deaminase, cytidine deaminase, or adenosine deaminase and cytidine deaminase) is inserted in regions of the Cas9 polypeptide comprising higher than average B-factors (*e.g.*, higher B factors compared to the total protein or the protein domain comprising the disordered region). Cas9 polypeptide positions comprising a higher than average B-factor can include, for example, residues 768,
 20 792, 1052, 1015, 1022, 1026, 1029, 1067, 1040, 1054, 1068, 1246, 1247, and 1248 as numbered in SEQ ID NO: 197. Cas9 polypeptide regions comprising a higher than average B-factor can include, for example, residues 792-872, 792-906, and 2-791 as numbered in SEQ ID NO: 197.

- In some embodiments, a heterologous polypeptide (*e.g.*, deaminase) is inserted in a
 25 flexible loop of a Cas9 polypeptide. The flexible loop portions can be selected from the group consisting of 530-537, 569-570, 686-691, 943-947, 1002-1025, 1052-1077, 1232-1247, or 1298-1300 as numbered in SEQ ID NO: 197, or a corresponding amino acid residue in another Cas9 polypeptide. The flexible loop portions can be selected from the group consisting of: 1-529, 538-568, 580-685, 692-942, 948-1001, 1026-1051, 1078-1231, or 1248-
 30 1297 as numbered in SEQ ID NO: 197, or a corresponding amino acid residue in another Cas9 polypeptide.

A heterologous polypeptide (*e.g.*, adenine deaminase) can be inserted into a Cas9 polypeptide region corresponding to amino acid residues: 1017-1069, 1242-1247, 1052-1056, 1060-1077, 1002 – 1003, 943-947, 530-537, 568-579, 686-691, 1242-1247, 1298 – 1300,

1066-1077, 1052-1056, or 1060-1077 as numbered in SEQ ID NO: 197, or a corresponding amino acid residue in another Cas9 polypeptide.

- A heterologous polypeptide (e.g., adenine deaminase) can be inserted in place of a deleted region of a Cas9 polypeptide. The deleted region can correspond to an N-terminal or C-terminal portion of the Cas9 polypeptide. Exemplary internal fusions base editors are provided in **Table 4A** below:

Table 4A: Insertion loci in Cas9 proteins

BE ID	Modification	Other ID
IBE001	Cas9 TadA ins 1015	ISLAY01
IBE002	Cas9 TadA ins 1022	ISLAY02
IBE003	Cas9 TadA ins 1029	ISLAY03
IBE004	Cas9 TadA ins 1040	ISLAY04
IBE005	Cas9 TadA ins 1068	ISLAY05
IBE006	Cas9 TadA ins 1247	ISLAY06
IBE007	Cas9 TadA ins 1054	ISLAY07
IBE008	Cas9 TadA ins 1026	ISLAY08
IBE009	Cas9 TadA ins 768	ISLAY09
IBE020	delta HNH TadA 792	ISLAY20
IBE021	N-term fusion single TadA helix truncated 165-end	ISLAY21
IBE029	TadA-Circular Permutant116 ins1067	ISLAY29
IBE031	TadA- Circular Permutant 136 ins1248	ISLAY31
IBE032	TadA- Circular Permutant 136ins 1052	ISLAY32
IBE035	delta 792-872 TadA ins	ISLAY35
IBE036	delta 792-906 TadA ins	ISLAY36
IBE043	TadA-Circular Permutant 65 ins1246	ISLAY43
IBE044	TadA ins C-term truncate2 791	ISLAY44

- A heterologous polypeptide (e.g., deaminase) can be inserted within a structural or functional domain of a Cas9 polypeptide. A heterologous polypeptide (e.g., deaminase) can be inserted between two structural or functional domains of a Cas9 polypeptide. A heterologous polypeptide (e.g., deaminase) can be inserted in place of a structural or functional domain of a Cas9 polypeptide, for example, after deleting the domain from the Cas9 polypeptide. The structural or functional domains of a Cas9 polypeptide can include, for example, RuvC I, RuvC II, RuvC III, Rec1, Rec2, PI, or HNH.

- A fusion protein can comprise a linker between the deaminase and the napDNAbp polypeptide. The linker can be a peptide or a non-peptide linker. For example, the linker can be an XTEN, (GGGS)_n (SEQ ID NO: 246), SGGSSGGGS (SEQ ID NO: 330), (GGGGS)_n (SEQ ID NO: 247), (G)_n, (EAAAK)_n (SEQ ID NO: 248), (GGS)_n, SGSETPGTSESATPES (SEQ ID

NO: 249). In some embodiments, the fusion protein comprises a linker between the N-terminal Cas9 fragment and the deaminase. In some embodiments, the fusion protein comprises a linker between the C-terminal Cas9 fragment and the deaminase. In some embodiments, the N-terminal and C-terminal fragments of napDNABp are connected to the deaminase with a linker. In some embodiments, the N-terminal and C-terminal fragments are joined to the deaminase domain without a linker. In some embodiments, the fusion protein comprises a linker between the N-terminal Cas9 fragment and the deaminase but does not comprise a linker between the C-terminal Cas9 fragment and the deaminase. In some embodiments, the fusion protein comprises a linker between the C-terminal Cas9 fragment and the deaminase but does not comprise a linker between the N-terminal Cas9 fragment and the deaminase.

In some embodiments, the napDNABp in the fusion protein or complex is a Cas12 polypeptide, *e.g.*, Cas12b/C2c1, or a functional fragment thereof capable of associating with a nucleic acid (*e.g.*, a gRNA) that guides the Cas12 to a specific nucleic acid sequence. The Cas12 polypeptide can be a variant Cas12 polypeptide. In other embodiments, the N- or C-terminal fragments of the Cas12 polypeptide comprise a nucleic acid programmable DNA binding domain or a RuvC domain. In other embodiments, the fusion protein contains a linker between the Cas12 polypeptide and the catalytic domain. In other embodiments, the amino acid sequence of the linker is GGSGGS (SEQ ID NO: 250) or GSSGSETPGTSESATPSSG (SEQ ID NO: 251). In other embodiments, the linker is a rigid linker. In other embodiments of the above aspects, the linker is encoded by GGAGGCTCTGGAGGAAGC (SEQ ID NO: 252) or GGCTCTTCTGGATCTGAAACACCTGGCACAAGCGAGAGCGCCACCCCTGAGAGCTCTGGC (SEQ ID NO: 253).

In other embodiments, the fusion protein or complex contains a nuclear localization signal (*e.g.*, a bipartite nuclear localization signal). In other embodiments, the amino acid sequence of the nuclear localization signal is MAPKKKRKVGIIHGVPAA (SEQ ID NO: 261). In other embodiments of the above aspects, the nuclear localization signal is encoded by the following sequence:

ATGGCCCCAAAGAAGAAGCGGAAGGTCGGTATCCACGGAGTCCCAGCAGCC (SEQ ID NO: 262). In other embodiments, the Cas12b polypeptide contains a mutation that silences the catalytic activity of a RuvC domain. In other embodiments, the Cas12b polypeptide contains D574A, D829A and/or D952A mutations.

In some embodiments, the fusion protein or complex comprises a napDNAbp domain (e.g., Cas12-derived domain) with an internally fused nucleobase editing domain (e.g., all or a portion (e.g., a functional portion) of a deaminase domain, e.g., an adenosine deaminase domain). In some embodiments, the napDNAbp is a Cas12b. In some embodiments, the base editor comprises a BhCas12b domain with an internally fused TadA*8 domain inserted at the loci provided in **Table 4B** below.

Table 4B: Insertion loci in Cas12b proteins

BhCas12b	Insertion site	Inserted between aa
position 1	153	PS
position 2	255	KE
position 3	306	DE
position 4	980	DG
position 5	1019	KL
position 6	534	FP
position 7	604	KG
position 8	344	HF
BvCas12b	Insertion site	Inserted between aa
position 1	147	PD
position 2	248	GG
position 3	299	PE
position 4	991	GE
position 5	1031	KM
AaCas12b	Insertion site	Inserted between aa
position 1	157	PG
position 2	258	VG
position 3	310	DP
position 4	1008	GE
position 5	1044	GK

In some embodiments, the base editing system described herein is an ABE with TadA inserted into a Cas9. Polypeptide sequences of relevant ABEs with TadA inserted into a Cas9 are provided in the attached Sequence Listing as SEQ ID NOs: 263-308.

Exemplary, yet nonlimiting, fusion proteins are described in International PCT Application Nos. PCT/US2020/016285 and U.S. Provisional Application Nos. 62/852,228 and 62/852,224, the contents of which are incorporated by reference herein in their entireties.

A to G Editing

In some embodiments, a base editor described herein comprises an adenosine deaminase domain. Such an adenosine deaminase domain of a base editor can facilitate the

editing of an adenine (A) nucleobase to a guanine (G) nucleobase by deaminating the A to form inosine (I), which exhibits base pairing properties of G. In some embodiments, an A-to-G base editor further comprises an inhibitor of inosine base excision repair, for example, a uracil glycosylase inhibitor (UGI) domain or a catalytically inactive inosine specific nuclease.

- 5 Without wishing to be bound by any particular theory, the UGI domain or catalytically inactive inosine specific nuclease can inhibit or prevent base excision repair of a deaminated adenosine residue (*e.g.*, inosine), which can improve the activity or efficiency of the base editor.

- A base editor comprising an adenosine deaminase can act on any polynucleotide, including DNA, RNA and DNA-RNA hybrids. In an embodiment an adenosine deaminase domain of a base editor comprises all or a portion (*e.g.*, a functional portion) of an ADAT comprising one or more mutations which permit the ADAT to deaminate a target A in DNA. For example, the base editor can comprise all or a portion (*e.g.*, a functional portion) of an ADAT from *Escherichia coli* (EcTadA) comprising one or more of the following mutations:
- 10 D108N, A106V, D147Y, E155V, L84F, H123Y, I156F, or a corresponding mutation in another adenosine deaminase. Exemplary ADAT homolog polypeptide sequences are provided in the Sequence Listing as SEQ ID NOs: 1 and 309-315.

- The adenosine deaminase can be derived from any suitable organism (*e.g.*, *E. coli*). In some embodiments, the adenosine deaminase is from *Escherichia coli*, *Staphylococcus aureus*, *Salmonella typhi*, *Shewanella putrefaciens*, *Haemophilus influenzae*, *Caulobacter crescentus*, or *Bacillus subtilis*. In some embodiments, the adenine deaminase is a naturally-occurring adenosine deaminase that includes one or more mutations corresponding to any of the mutations provided herein (*e.g.*, mutations in ecTadA). The corresponding residue in any homologous protein can be identified by *e.g.*, sequence alignment and determination of
- 20 homologous residues. The mutations in any naturally-occurring adenosine deaminase (*e.g.*, having homology to ecTadA) that correspond to any of the mutations described herein (*e.g.*, any of the mutations identified in ecTadA) can be generated accordingly.

- In some embodiments, the adenosine deaminase comprises an amino acid sequence that is at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 99.5% identical to any one of the amino acid sequences set forth in any of the adenosine deaminases provided herein. It should be appreciated that adenosine deaminases provided herein may include one or more mutations (*e.g.*, any of the mutations provided herein). The disclosure provides any deaminase domains with a certain percent identify plus any of the
- 30

mutations or combinations thereof described herein. In some embodiments, the adenosine deaminase comprises an amino acid sequence that has 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, or more mutations compared to a reference sequence, or any of the adenosine deaminases provided herein.

It should be appreciated that any of the mutations provided herein (*e.g.*, based on a TadA reference sequence, such as TadA*7.10 (SEQ ID NO: 1)) can be introduced into other adenosine deaminases, such as *E. coli* TadA (ecTadA), *S. aureus* TadA (saTadA), or other adenosine deaminases (*e.g.*, bacterial adenosine deaminases). In some embodiments, the TadA reference sequence is TadA*7.10 (SEQ ID NO: 1). It would be apparent to the skilled artisan that additional deaminases may similarly be aligned to identify homologous amino acid residues that can be mutated as provided herein. Thus, any of the mutations identified in a TadA reference sequence can be made in other adenosine deaminases (*e.g.*, ecTadA) that have homologous amino acid residues. It should also be appreciated that any of the mutations provided herein can be made individually or in any combination in a TadA reference sequence or another adenosine deaminase.

In some embodiments, the adenosine deaminase comprises an alteration or set of alterations selected from those listed in **Tables 5A-5G** below:

Table 5A. Adenosine Deaminase Variants. Residue positions in the *E. coli* TadA variant (TadA*) are indicated.

	23	26	36	37	48	49	51	72	84	87	106	108	123	125	142	146	147	152	155	156	157	161
TadA*0.1	W	R	H	N	P		R	N	L	S	A	D	H	G	A	S	D	R	E	I	K	K
TadA*0.2	W	R	H	N	P		R	N	L	S	A	D	H	G	A	S	D	R	E	I	K	K
TadA*1.1	W	R	H	N	P		R	N	L	S	A	N	H	G	A	S	D	R	E	I	K	K
TadA*1.2	W	R	H	N	P		R	N	L	S	V	N	H	G	A	S	D	R	E	I	K	K
TadA*2.1	W	R	H	N	P		R	N	L	S	V	N	H	G	A	S	Y	R	V	I	K	K
TadA*2.2	W	R	H	N	P		R	N	L	S	V	N	H	G	A	S	Y	R	V	I	K	K
TadA*2.3	W	R	H	N	P		R	N	L	S	V	N	H	G	A	S	Y	R	V	I	K	K
TadA*2.4	W	R	H	N	P		R	N	L	S	V	N	H	G	A	S	Y	R	V	I	K	K
TadA*2.5	W	R	H	N	P		R	N	L	S	V	N	H	G	A	S	Y	R	V	I	K	K
TadA*2.6	W	R	H	N	P		R	N	L	S	V	N	H	G	A	S	Y	R	V	I	K	K
TadA*2.7	W	R	H	N	P		R	N	L	S	V	N	H	G	A	S	Y	R	V	I	K	K
TadA*2.8	W	R	H	N	P		R	N	L	S	V	N	H	G	A	S	Y	R	V	I	K	K
TadA*2.9	W	R	H	N	P		R	N	L	S	V	N	H	G	A	S	Y	R	V	I	K	K
TadA*2.10	W	R	H	N	P		R	N	L	S	V	N	H	G	A	S	Y	R	V	I	K	K
TadA*2.11	W	R	H	N	P		R	N	L	S	V	N	H	G	A	S	Y	R	V	I	K	K
TadA*2.12	W	R	H	N	P		R	N	L	S	V	N	H	G	A	S	Y	R	V	I	K	K
TadA*3.1	W	R	H	N	P		R	N	F	S	V	N	Y	G	A	S	Y	R	V	F	K	K

	23	26	36	37	48	49	51	72	84	87	106	108	123	125	142	146	147	152	155	156	157	161
TadA*3.2	W	R	H	N	P		R	N	F	S	V	N	Y	G	A	S	Y	R	V	F	K	K
TadA*3.3	W	R	H	N	P		R	N	F	S	V	N	Y	G	A	S	Y	R	V	F	K	K
TadA*3.4	W	R	H	N	P		R	N	F	S	V	N	Y	G	A	S	Y	R	V	F	K	K
TadA*3.5	W	R	H	N	P		R	N	F	S	V	N	Y	G	A	S	Y	R	V	F	K	K
TadA*3.6	W	R	H	N	P		R	N	F	S	V	N	Y	G	A	S	Y	R	V	F	K	K
TadA*3.7	W	R	H	N	P		R	N	F	S	V	N	Y	G	A	S	Y	R	V	F	K	K
TadA*3.8	W	R	H	N	P		R	N	F	S	V	N	Y	G	A	S	Y	R	V	F	K	K
TadA*4.1	W	R	H	N	P		R	N	L	S	V	N	H	G	N	S	Y	R	V	I	K	K
TadA*4.2	W	G	H	N	P		R	N	L	S	V	N	H	G	N	S	Y	R	V	I	K	K
TadA*4.3	W	R	H	N	P		R	N	F	S	V	N	Y	G	N	S	Y	R	V	F	K	K
TadA*5.1	W	R	L	N	P		L	N	F	S	V	N	Y	G	A	C	Y	R	V	F	N	K
TadA*5.2	W	R	H	S	P		R	N	F	S	V	N	Y	G	A	S	Y	R	V	F	K	T
TadA*5.3	W	R	L	N	P		L	N	I	S	V	N	Y	G	A	C	Y	R	V	F	N	K
TadA*5.4	W	R	H	S	P		R	N	F	S	V	N	Y	G	A	S	Y	R	V	F	K	T
TadA*5.5	W	R	L	N	P		L	N	F	S	V	N	Y	G	A	C	Y	R	V	F	N	K
TadA*5.6	W	R	L	N	P		L	N	F	S	V	N	Y	G	A	C	Y	R	V	F	N	K
TadA*5.7	W	R	L	N	P		L	N	F	S	V	N	Y	G	A	C	Y	R	V	F	N	K
TadA*5.8	W	R	L	N	P		L	N	F	S	V	N	Y	G	A	C	Y	R	V	F	N	K
TadA*5.9	W	R	L	N	P		L	N	F	S	V	N	Y	G	A	C	Y	R	V	F	N	K
TadA*5.10	W	R	L	N	P		L	N	F	S	V	N	Y	G	A	C	Y	R	V	F	N	K
TadA*5.11	W	R	L	N	P		L	N	F	S	V	N	Y	G	A	C	Y	R	V	F	N	K
TadA*5.12	W	R	L	N	P		L	N	F	S	V	N	Y	G	A	C	Y	R	V	F	N	K
TadA*5.13	W	R	H	N	P		L	D	F	S	V	N	Y	A	A	S	Y	R	V	F	K	K
TadA*5.14	W	R	H	N	S		L	N	F	C	V	N	Y	G	A	S	Y	R	V	F	K	K
TadA*6.1	W	R	H	N	S		L	N	F	S	V	N	Y	G	N	S	Y	R	V	F	K	K
TadA*6.2	W	R	H	N	T	V	L	N	F	S	V	N	Y	G	N	S	Y	R	V	F	N	K
TadA*6.3	W	R	L	N	S		L	N	F	S	V	N	Y	G	A	C	Y	R	V	F	N	K
TadA*6.4	W	R	L	N	S		L	N	F	S	V	N	Y	G	N	C	Y	R	V	F	N	K
TadA*6.5	W	R	L	N	T	V	L	N	F	S	V	N	Y	G	A	C	Y	R	V	F	N	K
TadA*6.6	W	R	L	N	T	V	L	N	F	S	V	N	Y	G	N	C	Y	R	V	F	N	K
TadA*7.1	W	R	L	N	A		L	N	F	S	V	N	Y	G	A	C	Y	R	V	F	N	K
TadA*7.2	W	R	L	N	A		L	N	F	S	V	N	Y	G	N	C	Y	R	V	F	N	K
TadA*7.3	L	R	L	N	A		L	N	F	S	V	N	Y	G	A	C	Y	R	V	F	N	K
TadA*7.4	R	R	L	N	A		L	N	F	S	V	N	Y	G	A	C	Y	R	V	F	N	K
TadA*7.5	W	R	L	N	A		L	N	F	S	V	N	Y	G	A	C	Y	H	V	F	N	K
TadA*7.6	W	R	L	N	A		L	N	I	S	V	N	Y	G	A	C	Y	P	V	F	N	K
TadA*7.7	L	R	L	N	A		L	N	F	S	V	N	Y	G	A	C	Y	P	V	F	N	K
TadA*7.8	L	R	L	N	A		L	N	F	S	V	N	Y	G	N	C	Y	R	V	F	N	K
TadA*7.9	L	R	L	N	A		L	N	F	S	V	N	Y	G	N	C	Y	P	V	F	N	K
TadA*7.10	R	R	L	N	A		L	N	F	S	V	N	Y	G	A	C	Y	P	V	F	N	K

Table 5B. TadA*8 Adenosine Deaminase Variants. Residue positions in the *E. coli* TadA variant (TadA*) are indicated. Alterations are referenced to TadA*7.10 (first row).

	2	3	4	5	7	8	8	10	10	12	14	14	15	15	15	15	15	166
TadA*7.10	R	L	A	L	I	V	F	V	N	Y	C	Y	P	Q	V	F	N	T

TadA*8.1												T						
TadA*8.2												R						
TadA*8.3														S				
TadA*8.4										H								
TadA*8.5						S												
TadA*8.6																		R
TadA*8.7														R				
TadA*8.8										H		R		R				
TadA*8.9					Y							R		R				
TadA*8.10												R		R				R
TadA*8.11												T		R				
TadA*8.12												T		S				
TadA*8.13					Y					H		R		R				
TadA*8.14					Y	S												
TadA*8.15						S						R						
TadA*8.16						S				H		R						
TadA*8.17						S								R				
TadA*8.18						S				H				R				
TadA*8.19						S				H		R		R				
TadA*8.20					Y	S				H		R		R				
TadA*8.21												R		S				
TadA*8.22						S								S				
TadA*8.23						S				H								
TadA*8.24						S				H		T						

Table 5C. TadA*9 Adenosine Deaminase Variants. Alterations are referenced to TadA*7.10. Additional details of TadA*9 adenosine deaminases are described in International PCT Application No. PCT/US2020/049975, which is incorporated herein by reference in its entirety for all purposes.

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TadA*9 Description	Alterations
TadA*9.1	E25F, V82S, Y123H, T133K, Y147R, Q154R
TadA*9.2	E25F, V82S, Y123H, Y147R, Q154R
TadA*9.3	V82S, Y123H, P124W, Y147R, Q154R
TadA*9.4	L51W, V82S, Y123H, C146R, Y147R, Q154R
TadA*9.5	P54C, V82S, Y123H, Y147R, Q154R
TadA*9.6	Y73S, V82S, Y123H, Y147R, Q154R
TadA*9.7	N38G, V82T, Y123H, Y147R, Q154R
TadA*9.8	R23H, V82S, Y123H, Y147R, Q154R
TadA*9.9	R21N, V82S, Y123H, Y147R, Q154R
TadA*9.10	V82S, Y123H, Y147R, Q154R, A158K
TadA*9.11	N72K, V82S, Y123H, D139L, Y147R, Q154R,
TadA*9.12	E25F, V82S, Y123H, D139M, Y147R, Q154R
TadA*9.13	M70V, V82S, M94V, Y123H, Y147R, Q154R
TadA*9.14	Q71M, V82S, Y123H, Y147R, Q154R

TadA*9.15	E25F, V82S, Y123H, T133K, Y147R, Q154R
TadA*9.16	E25F, V82S, Y123H, Y147R, Q154R
TadA*9.17	V82S, Y123H, P124W, Y147R, Q154R
TadA*9.18	L51W, V82S, Y123H, C146R, Y147R, Q154R
TadA*9.19	P54C, V82S, Y123H, Y147R, Q154R
TadA*9.2	Y73S, V82S, Y123H, Y147R, Q154R
TadA*9.21	N38G, V82T, Y123H, Y147R, Q154R
TadA*9.22	R23H, V82S, Y123H, Y147R, Q154R
TadA*9.23	R21N, V82S, Y123H, Y147R, Q154R
TadA*9.24	V82S, Y123H, Y147R, Q154R, A158K
TadA*9.25	N72K, V82S, Y123H, D139L, Y147R, Q154R,
TadA*9.26	E25F, V82S, Y123H, D139M, Y147R, Q154R
TadA*9.27	M70V, V82S, M94V, Y123H, Y147R, Q154R
TadA*9.28	Q71M, V82S, Y123H, Y147R, Q154R
TadA*9.29	E25F, I76Y, V82S, Y123H, Y147R, Q154R
TadA*9.30	I76Y, V82T, Y123H, Y147R, Q154R
TadA*9.31	N38G, I76Y, V82S, Y123H, Y147R, Q154R
TadA*9.32	N38G, I76Y, V82T, Y123H, Y147R, Q154R
TadA*9.33	R23H, I76Y, V82S, Y123H, Y147R, Q154R
TadA*9.34	P54C, I76Y, V82S, Y123H, Y147R, Q154R
TadA*9.35	R21N, I76Y, V82S, Y123H, Y147R, Q154R
TadA*9.36	I76Y, V82S, Y123H, D138M, Y147R, Q154R
TadA*9.37	Y72S, I76Y, V82S, Y123H, Y147R, Q154R
TadA*9.38	E25F, I76Y, V82S, Y123H, Y147R, Q154R
TadA*9.39	I76Y, V82T, Y123H, Y147R, Q154R
TadA*9.40	N38G, I76Y, V82S, Y123H, Y147R, Q154R
TadA*9.41	N38G, I76Y, V82T, Y123H, Y147R, Q154R
TadA*9.42	R23H, I76Y, V82S, Y123H, Y147R, Q154R
TadA*9.43	P54C, I76Y, V82S, Y123H, Y147R, Q154R
TadA*9.44	R21N, I76Y, V82S, Y123H, Y147R, Q154R
TadA*9.45	I76Y, V82S, Y123H, D138M, Y147R, Q154R
TadA*9.46	Y72S, I76Y, V82S, Y123H, Y147R, Q154R
TadA*9.47	N72K, V82S, Y123H, Y147R, Q154R
TadA*9.48	Q71M, V82S, Y123H, Y147R, Q154R
TadA*9.49	M70V, V82S, M94V, Y123H, Y147R, Q154R
TadA*9.50	V82S, Y123H, T133K, Y147R, Q154R
TadA*9.51	V82S, Y123H, T133K, Y147R, Q154R, A158K
TadA*9.52	M70V, Q71M, N72K, V82S, Y123H, Y147R, Q154R
TadA*9.53	N72K, V82S, Y123H, Y147R, Q154R
TadA*9.54	Q71M, V82S, Y123H, Y147R, Q154R
TadA*9.55	M70V, V82S, M94V, Y123H, Y147R, Q154R
TadA*9.56	V82S, Y123H, T133K, Y147R, Q154R
TadA*9.57	V82S, Y123H, T133K, Y147R, Q154R, A158K
TadA*9.58	M70V, Q71M, N72K, V82S, Y123H, Y147R, Q154R

In some embodiments, the adenosine deaminase comprises a TadA*8.20 adenosine deaminase variant further comprising an F149Y amino acid alteration. In some embodiments,

the adenosine deaminase comprises a TadA*8.20 adenosine deaminase variant further comprising the amino acid alterations R147D, F149Y, T166I, and D167N (TadA*8.10+). In some embodiments, the adenosine deaminase comprises a TadA*8.20 adenosine deaminase variant further comprising the amino acid alterations S82T and F149Y (TadA*9v1). In some
 5 embodiments, the adenosine deaminase comprises a TadA*8.20 adenosine deaminase variant further comprising the amino acid alterations Y147D, F149Y, T166I, D167N and S82T (TadA*9v2).

In some embodiments, the adenosine deaminase comprises one or more of M1I, M1S, S2A, S2E, S2H, S2R, S2L, E3L, V4D, V4E, V4M, V4K, V4S, V4T, V4A, E5K, F6S, F6G,
 10 F6H, F6Y, F6I, F6E, S7K, H8E, H8Y, H8H, H8Q, H8E, H8G, H8S, E9Y, E9K, E9V, E9E, Y10F, Y10W, Y10Y, M12S, M12L, M12R, M12W, R13H, R13I, R13Y, R13R, R13G, R13S, H14N, A15D, A15V, A15L, A15H, T17T, T17A, T17W, T17L, T17F, T17R, T17S, L18A, L18E, L18N, L18L, L18S, A19N, A19H, A19K, A19A, A19D, A19G, A19M, R21N, K20K, K20A, K20R, K20E, K20G, K20C, K20Q R21A, R21R, R21N, R21Y, R21C G22P,
 15 A22W, A22R, W23D, R23H, W23G, W23Q, W23L, W23R, W23H W23D W23M, W23W, W23I, D24E, D24G, D24W, D24D, D24R, E25F, E25M, E25D, E25A, E25G, E25R, E25E, E25H E25V, E25S, E25Y, R26D, R26E, R26G, R26N, R26Q, R26C, R26L, R26K, R26W, R26C, R26P, R26R, R26A, R26H, E27E, E27Q, E27H, E27C, E27G, E27K, E27S, E27P, E27R, E27L, E27V, E27D, V28V, V28A, V28C, V28G, V28P, V28S, V28T, P29V, P29P,
 20 P29A, P29G, P29K, P29L, V30V, V30I, V30L, V30F, V30G, V30A, V30M, L34S, L34V, L34L, L34M, L34W, L34G, H36E, H36V, L36H, H36L, H36N, N37N, N37H, N37R, N37T, N37S, N38G, N38R, N38N, N38E, V40I, W45A, W45W, W45R, W45L, W45N, N46N, N46M, N46P, N46G, N46L, N46R, N46V, R46W, R46F, R46Q, R46M, R47A, R47Q, R47F, R47K, R47P, R47W, R47M, R47R, R47G, R47S, R47V, R47H, P48T, P48L, P48A, P48I,
 25 P48S, P48R, P48K, P48D, P48E, P48H, P48G, P48P, P48N, I49G, I49H, I49V, I49F, I49H, I49I, I49M, I49N, I49K, I49Q, I49T, G50L, G50S, G50R, G50G, R51H, R51L, R51N, L51W, R51Y, R51G, R51V, R51R, H52D, H52Y, H52I, H52H, D53D, D53E, D53G, D53P, P54C, P54T, P54P, P54E, A55H, T55A, T55I, T55V, T55G, T55T, A56A, A56H, A56W, A56E, A56S, H57P, H57A, H57H, H57N, A58G, A58E, A58A, A58R, E59A, E59G, E59I,
 30 E59Q, E59W, E59E, E59T, E59H, E59P, M61A, M61I, M61L, M61V, M61P, M61G, M61I, L63S, L63V, L63T, L63R, L63H, L63A, R64A, R64Q, R64R, R64D, Q65V, Q65H, Q65G, Q65P, Q65F, Q65Q, Q65R, G66V, G66E, G66T, G66G, G66C, G67G, G67W, G67I, G67A, G67D, G67L, G67V, L68Q, L68M, L68V, L68H, L68L, L68G, V69A, V69M, V69V, M70V, M70L, E70A, M70A, M70M, M70E, M70T, M70v, Q71M, Q71N, Q71L, Q71R,

Q71Q, Q71I, N72A, N72K, N72S, N72D, N72Y, N72N, N72H, N72G, N72M, Y73G, Y73I,
Y73K, Y73R, Y73S, Y73Y, Y73H, Y73A, R74A, R74Q, R74G, R74K, R74L, R74N, R74G,
R74K, R74R, I76H, I76R, I76W, I76Y, I76V, I76Q, I76L, I76D, I76F, I76I, I76N, I76T,
I76Y, D77G, D77D, D77A, D77Q, A78Y, A78T, A78G, A78A, A78I, T79M, T79R, T79L,
5 T79T, L80M, L80Y, L80I, L80V, L80L, Y81D, Y81V, Y81Y, Y81M, V82A, V82S, V82G,
V82T, V82V, V82Q, V82Y, T83L, T83F, T83T, T83N, L84E, L84F, L84Y, L84I, L84L,
L84M, L84A, L84T, L84S, E85K, E85G, E85P, E85S, E85E, E85F, E85V, E85R, P86T,
P86C, P86P, P86L, P86N, P86K, P86H, C87M, C87I, C87S, C87N, C87P, S87C, S87L,
S87V, V88A, V88M, V88V, V88T, V88E, V88D, V88S, C90S, C90P, C90A, C90T,
10 C90M, A91A, A91G, A91S, A91V, A91T, A91C, A91L, G92T, G92M, G92A, G92Y,
G92G, A93I, A93C, A93M, A93V, A93A, M94M, M94T, M94A, M94V, M94L, M94I,
M94H, I95S, I95G, I95L, I95H, I95V, H96A, H96L, H96R, H96S, H96H, H96N, H96E,
S97C, S97G, S97I, S97M, S97R, S97S, S97P, R98K, R98I, R98N, R98Q, R98G, R98H,
R98C, R98L, R98R, G100R, G100V, G100K, G100A, G100S, G100M, G100I, R101V,
15 R101R, R101S, R101C, V102A, V102F, V102I, V102V, D103A, V103A, V103G, V103F,
V103V, F104G, D104N, F104V, F104I, F104L, F104A, F104F, F104R, G105V, G105W,
G105G, G105M, G105A, A106T, V106Q, V106F, V106W, V106M, A106A, A106Q,
A106F, A106G, A106W, A106M, A106V, A106R, A106L, A106S, A106B, A106I, R107C,
R107G, R107P, R107K, R107A, R107N, R107W, R107H, R107S, R107R, R107F, D108N,
20 D108F, D108G, D108V, D108A, D108Y, D108H, D108I, D108K, D108L, D108M, D108Q,
N108Q, N108F, N108W, N108M, N108K, D108K, D108F, D108M, D108Q, D108R,
D108W, D108S, D108E, D108T, D108R, D108D, A109H, A109K, A109R, A109S, A109T,
A109V, A109A, A109D, K110G, K110H, K110I, K110R, K110T, K110K, K110A, K110I,
T111A, T111G, T111H, T111R, T111T, T111K, G112A, G112G, G112H, G112T, G112R,
25 A113N, A114G, A114H, A114V, A114C, A114S, A114A, G115S, G115G, G115M, G115L,
G115A, G115F, L117M, L117L, L117W, L117A, L117S, L117N, L117V, M118D, M118G,
M118K, M118N, M118V, M118M, M118L, M118R, D119L, D119N, D119S, D119V,
D119D, V120H, V120L, V120V, V120T, V120A, V120E, V120G, V120D, L121D, L121M,
L121N, L121K, L121L, H122H, H122N, H122P, H122R, H122S, H122Y, H122G, H122T,
30 H122L, H123C, H123G, H123P, H123V, H123Y, Y123H, H123Y, H123H, P124P, P124H,
P124A, P124Y, P124D, P124G, P124I, P124L, P124W, G125H, G125I, G125A, G125M,
G125K, G125G, G125P, M126D, M126H, M126K, M126I, M126N, M126O, M126S,
M126Y, M126M, M126G, N127H, N127S, N127D, N127K, N127R, N127N, N127I, N127P,
N127M, H128R, H128N, H128L, H128H, R129H, R129Q, R129V, R129I, R129E, R129V,

R129R, R129M, R129P, V130R, V130V, V130E, V130D, E131E, E131I, E131V, E131K,
 I132I, I132F, I132T, I132L, I132V, I132E, T133V, T133E, T133G, T133K, T133T, T133A,
 T133H, T133F, T133I, E134A, E134E, E134G, E134I, E134H, E134K, E134T, G135G,
 G135V, G135I, G135P, G135E, I136G, I136L, I136T, I136I, I137A, I137D, I137E, L137M,
 5 I137S, L137L, L137I, A138D, A138E, A138G, S138A, A138N, A138S, A138T, A138V,
 A138Y, A138A, A138M, A138L, D139E, D139I, D139C, D139L, D139M, D139D, D139G,
 D139H, D139A, E140A, E140C, E140L, E140R, E140K, E140E, E140D, C141S, C141A,
 C141C, C141V, C141E, A142N, A142D, A142G, A142A, A142L, A142S, A142T, A142N,
 A142S, A142V, A142E, A142C, A143D, A143E, A143G, , A143D, A143G, A143E, A143L,
 10 A143W, A143M, A143S, A143Q, A143R, A143A, A143I, L144S, L144L, L144T, L144A,
 L145A, L145F, L145G, L145D, L145L, L145C, L145E, L145s, C146R, S146A, S146C,
 S146D, S146F, S146R, S146T, S146D, S146G, S146S, S146L, D147D, D147L, D147F,
 D147G, D147Y, Y147T, Y147R, Y147D, D147R, D147Y, D147A, D147T, D147H, D147F,
 D147U, D147V, D147I, D147C, F148L, F148F, F148R, F148Y, F148A, F148T, F149C,
 15 F149M, F149R, F149Y, F149N, F149F, F149A, F149T, F149V R150R, R150M, R150D,
 R150F, M151E, M151P, M151R, M151V, M151M, M151E, R152C, R152F, R152H, R152P,
 R152R, R152P, R152Q, R152M, R152O, R153C, R153Q, R153R, R153V, R153E, R153A,
 R153P, Q154E, Q154H, Q154M, Q154R, Q154L, Q154S, Q154V, Q154Q, Q154F, Q154I,
 Q154A, Q154K, E155F, E155G, E155I, E155K, E155P, E155V, E155D, E155E, E155L,
 20 E155Q, I156V, I156A, I156I, I156L, I156F, I156D, I156K, I156N, I156R, I156Y, E157A,
 E157F, E157I, E157P, E157T, E157V, N157K, K157N, K157V, K157P, K157I, K157F,
 K157F, K157T, K157A, K157S, K157R, A158Q, A158K, A158V, A158A, A158D, A158S,
 A158T, A158N, Q159S, Q159Q, Q159A, Q159F, Q159K, Q159L, Q159N, K160A, K160S,
 K160E, K160K, K160N, K160F, K160Q, K161T, K161K, K161R, K161I, K161A, K161N,
 25 K161Q, K161S, K161T, A162D, A162Q, R162H, R162P, A162S, A162A, A162N, A162M,
 A162K, Q163G, Q163S, Q163Q, Q163A, Q163H, Q163N, Q163R, S164F, S164S, S164Q,
 S164I, S164R, S164Y, S165S, S165P, S165Q, S165A, S165D, S165I, S165T, S165Y,
 T166T, T166Q, T166E, T166S, T166D, T166K, T166I, T166N, T166P, T166R, D167S
 D167D, D167I, D167G, D167T, D167A and/or D167N mutation in a TadA reference
 30 sequence (e.g., TadA*7.10, ecTadA, or TadA8e), and any alternative mutation at the
 corresponding position, or one or more corresponding mutations in another adenosine
 deaminase. Additional mutations are described in U.S. Patent Application Publication No.
 2022/0307003 A1 U.S. Patent No. 11,155,803, and International Patent Application
 Publications No. WO 2023/288304 A2, PCT/CN2022/143408, WO 2018/027078 A1, WO

2021/158921 A1 and WO 2023/034959 A2, the disclosures of which are incorporated herein by reference in their entirety for all purposes.

In various embodiments, an adenosine deaminase of the disclosure lacks an N-terminal methionine.

5 In some embodiments, the disclosure provides TadA variants comprising an alteration at an amino acid selected from one or more of L36, I76, V82, Y147, Q154, and N157 compared to TadA*7.10. In some embodiments, the disclosure provides TadA variants comprising one or more of the following alterations relative to TadA*7.10: L36H, I76Y, V82T, Y147T, Q154S, and N157K. In some embodiments, the disclosure provides TadA
10 variants comprising the following alterations relative to TadA*7.10: L36H, I76Y, V82T, Y147T, Q154S, and N157K. In some embodiments, the disclosure provides TadA variants comprising the following alterations relative to TadA*7.10: F84Y, A109L, A109V, A109I, A109F, A109S, A109T, A109N, V155S, V155T, V155N, F156Y, F156W, F156R, F156N, and F156Q. In some embodiments, the disclosure provides TadA variants comprising the
15 following alterations relative to TadA*7.10: E3N, E3K, E3G, F6A, H14D, L18A, W23I, W23R, P29T, P29Y, P29Q, V35Q, L36S, N38D, G42M, N46Y, P48A, G50A, H52L, A62V, L63R, L63F, Q65R, G67N, L68V, M70I, N72Y, T79H, Y81V, V82S, M94R, G100V, V102E, V102S, R107A, A114C, G115E, M118L, D119L, H122T, P124H, P124K, P124Q, H128R, V130F, I132K, I132T, E140L, A142N, A142S, L144Q, L145R, L145N, Y147A,
20 F149A, R152P, F156N, and K160E.

In some embodiments, the disclosure provides TadA variants comprising a V82T, Y147T, and/or a Q154S mutation. In some embodiments, the disclosure provides TadA variants comprising a V82T, Y147T, and/or a Q154S mutation. In some embodiments, the disclosure provides TadA*8.8 further comprising a V82T mutation. In some embodiments,
25 the disclosure provides TadA*8.8 further comprising a V82T, a Y147T, and a Q154S mutation. In some embodiments, the disclosure provides TadA*8.17 further comprising a V82T mutation. In some embodiments, the disclosure provides TadA*8.17 further comprising a V82T, a Y147T, and a Q154S mutation. In some embodiments, the disclosure provides TadA*8.20 further comprising a V82T mutation. In some embodiments, the
30 disclosure provides TadA*8.20 further comprising a V82T, a Y147T, and a Q154S mutation.

In embodiments, a variant of TadA*7.10 comprises one or more alterations selected from any of those alterations provided herein.

In particular embodiments, an adenosine deaminase heterodimer comprises a TadA*8 domain and an adenosine deaminase domain selected from *Staphylococcus aureus* (*S. aureus*)

TadA, *Bacillus subtilis* (*B. subtilis*) TadA, *Salmonella typhimurium* (*S. typhimurium*) TadA, *Shewanella putrefaciens* (*S. putrefaciens*) TadA, *Haemophilus influenzae* F3031 (*H. influenzae*) TadA, *Caulobacter crescentus* (*C. crescentus*) TadA, *Geobacter sulfurreducens* (*G. sulfurreducens*) TadA, or TadA*7.10.

- 5 In some embodiments, the TadA*8 is a variant as shown in **Table 5D**. **Table 5D** shows certain amino acid position numbers in the TadA amino acid sequence and the amino acids present in those positions in the TadA-7.10 adenosine deaminase. **Table 5D** also shows amino acid changes in TadA variants relative to TadA-7.10 following phage-assisted non-continuous evolution (PANCE) and phage-assisted continuous evolution (PACE), as
- 10 described in M. Richter *et al.*, 2020, Nature Biotechnology, doi.org/10.1038/s41587-020-0453-z, the entire contents of which are incorporated by reference herein. In some embodiments, the TadA*8 is TadA*8a, TadA*8b, TadA*8c, TadA*8d, or TadA*8e. In some embodiments, the TadA*8 is TadA*8e. In one embodiment, an adenosine deaminase is a TadA*8 that comprises or consists essentially of SEQ ID NO: 316 or a fragment thereof
- 15 having adenosine deaminase activity.

Table 5D. Select TadA*8 Variants

		TadA amino acid number									
	TadA	26	88	109	111	119	122	147	149	166	167
	TadA-7.10	R	V	A	T	D	H	Y	F	T	D
PANCE 1					R						
PANCE 2				S/T	R						
PACE	TadA-8a	C		S	R	N	N	D	Y	I	N
	TadA-8b		A	S	R	N	N		Y	I	N
	TadA-8c	C		S	R	N	N		Y	I	N
	TadA-8d		A		R	N			Y		
	TadA-8e			S	R	N	N	D	Y	I	N

- In some embodiments, the TadA variant is a variant as shown in **Table 5E**. **Table 5E** shows certain amino acid position numbers in the TadA amino acid sequence and the amino acids present in those positions in the TadA*7.10 adenosine deaminase. In some
- 20 embodiments, the TadA variant is MSP605, MSP680, MSP823, MSP824, MSP825, MSP827, MSP828, or MSP829. In some embodiments, the TadA variant is MSP828. In some
- embodiments, the TadA variant is MSP829.

25

Table 5E. TadA Variants

Variant	TadA Amino Acid Number							
	36	76	82	147	149	154	157	167
TadA-7.10	L	I	V	Y	F	Q	N	D
MSP605			G	T		S		
MSP680		Y	G	T		S		
MSP823	H		G	T		S	K	
MSP824			G	D	Y	S		N
MSP825	H		G	D	Y	S	K	N
MSP827	H	Y	G	T		S	K	
MSP828		Y	G	D	Y	S		N
MSP829	H	Y	G	D	Y	S	K	N

Table 5F. TadA Variants

Description										
Amino Acid No.	23	36	48	51	76	82	84	106	108	123
TadA (wt)	W	H	P	R	I	V	L	A	D	H
TadA*7.10	R	L	A	L	I	V	F	V	N	Y
TadA*8.8										H
TadA*8.13					Y					H
TadA*8.17						S				
TadA*8.20					Y	S				H
TadA*8.8 +V82T						T				H
TadA*8.8 +V82T+Y147T+Q154S						T				H
TadA*8.17 +V82T						T				
TadA*8.17 +V82T+Y147T+Q154S						T				
TadA*8.20 +V82T					Y	T				H
TadA*8.20 +V82T+Y147T+Q154S					Y	T				H

Table 5F (CONTINUED). TadA Variants

Official Name									
Amino Acid No.	146	147	152	154	155	156	157	166	
TadA (wt)	S	D	R	Q	E	I	K	T	
TadA*7.10	C	Y	P	Q	V	F	N	T	
TadA*8.8		R		R					
TadA*8.13		R		R					
TadA*8.17				R					
TadA*8.20		R		R					
TadA*8.8 +V82T		R		R					
TadA*8.8 +V82T+Y147T+Q154S		T		S					
TadA*8.17 +V82T				R					
TadA*8.17 +V82T+Y147T+Q154S		T		S					
TadA*8.20 +V82T		R		R					
TadA*8.20 +V82T+Y147T+Q154S		T		S					

Table 5G. TadA Variants

Official Name	Alternative Name	7 6	8 2	8 4	10 9	11 1	11 9	12 2	12 3	14 6	14 7	14 9	15 4	15 5	15 6	16 6	16 7
TadA (wt)		I	V	L	A	T	D	H	H	S	D	F	Q	E	I	T	D
ABE7.10		I	V	F	A	T	D	H	Y	C	Y	F	Q	V	F	T	D
8.8 + V82T			T						H		R		R				
8.8 + V82T + Y147T + Q154S			T						H		T		S				
8.17 + V82T			T										R				

Official Name	Alternative Name	7 6	8 2	8 4	10 9	11 1	11 9	12 2	12 3	14 6	14 7	14 9	15 4	15 5	15 6	16 6	16 7
8.17 + V82T + Y147T + Q154S			T								T		S				
8.20 + V82T		Y	T						H		R		R				
8.20 + V82T + Y147T + Q154S		Y	T						H		T		S				
ABE8e					S	R	N	N			D	Y	Q			I	N
ABE9.1e	8.20 + V82T + F149Y	Y	T						H		R	Y	R				
ABE9.2e	8.20 + V82T + Y147D + F149Y + T166I + D167N	Y	T						H		D	Y	R			I	N
ABE-301		Y	G								D	Y	S				N
TTR	8.20 + A109L + V155S	Y	S		L				H		R		R	S			
TTR	F84Y + F156N	Y	S	Y					H		R		R		N		

In particular embodiments, the fusion proteins or complexes comprise a single (*e.g.*, provided as a monomer) TadA* (*e.g.*, TadA*8 or TadA*9). Throughout the present disclosure, an adenosine deaminase base editor that comprises a single TadA* domain is

5 indicates using the terminology ABEm or ABE#m, where “#” is an identifying number (*e.g.*, ABE8.20m), where “m” indicates “monomer.” In some embodiments, the TadA* is linked to a Cas9 nickase. In some embodiments, the fusion proteins or complexes of the disclosure comprise as a heterodimer of a wild-type TadA (TadA(wt)) linked to a TadA*. Throughout the present disclosure, an adenosine deaminase base editor that comprises a single TadA*

10 domain and a TadA(wt) domain is indicates using the terminology ABEd or ABE#d, where “#” is an identifying number (*e.g.*, ABE8.20d), where “d” indicates “dimer.” In other embodiments, the fusion proteins or complexes of the disclosure comprise as a heterodimer of a TadA*7.10 linked to a TadA*. In some embodiments, the base editor is ABE8 comprising a TadA* variant monomer. In some embodiments, the base editor is ABE

15 comprising a heterodimer of a TadA* and a TadA(wt). In some embodiments, the base editor is ABE comprising a heterodimer of a TadA* and TadA*7.10. In some embodiments, the

base editor is ABE comprising a heterodimer of a TadA*. In some embodiments, the TadA* is selected from **Tables 5A-5E**.

In some embodiments, the adenosine deaminase is expressed as a monomer. In other embodiments, the adenosine deaminase is expressed as a heterodimer. In some embodiments, the deaminase or other polypeptide sequence lacks a methionine, for example when included as a component of a fusion protein. This can alter the numbering of positions. However, the skilled person will understand that such corresponding mutations refer to the same mutation.

Any of the mutations provided herein and any additional mutations (*e.g.*, based on the ecTadA amino acid sequence) can be introduced into any other adenosine deaminases. Any of the mutations provided herein can be made individually or in any combination in a TadA reference sequence or another adenosine deaminase (*e.g.*, ecTadA).

Details of A to G nucleobase editing proteins are described in International PCT Application No. PCT/US2017/045381 (WO2018/027078) and Gaudelli, N.M., *et al.*, “Programmable base editing of A•T to G•C in genomic DNA without DNA cleavage” Nature, 551, 464-471 (2017), the entire contents of which are hereby incorporated by reference.

C to T Editing

In some embodiments, a base editor disclosed herein comprises a fusion protein or complex comprising cytidine deaminase capable of deaminating a target cytidine (C) base of a polynucleotide to produce uridine (U), which has the base pairing properties of thymine. In some embodiments, for example where the polynucleotide is double-stranded (*e.g.*, DNA), the uridine base can then be substituted with a thymidine base (*e.g.*, by cellular repair machinery) to give rise to a C:G to a T:A transition. In other embodiments, deamination of a C to U in a nucleic acid by a base editor cannot be accompanied by substitution of the U to a T.

The deamination of a target C in a polynucleotide to give rise to a U is a non-limiting example of a type of base editing that can be executed by a base editor described herein. In another example, a base editor comprising a cytidine deaminase domain can mediate conversion of a cytosine (C) base to a guanine (G) base. For example, a U of a polynucleotide produced by deamination of a cytidine by a cytidine deaminase domain of a base editor can be excised from the polynucleotide by a base excision repair mechanism (*e.g.*, by a uracil DNA glycosylase (UDG) domain), producing an abasic site. The nucleobase opposite the abasic site can then be substituted (*e.g.*, by base repair machinery) with another base, such as

a C, by for example a translesion polymerase. Although it is typical for a nucleobase opposite an abasic site to be replaced with a C, other substitutions (*e.g.*, A, G or T) can also occur.

Accordingly, in some embodiments a base editor described herein comprises a deamination domain (*e.g.*, cytidine deaminase domain) capable of deaminating a target C to a U in a polynucleotide. Further, as described below, the base editor can comprise additional domains which facilitate conversion of the U resulting from deamination to, in some embodiments, a T or a G. For example, a base editor comprising a cytidine deaminase domain can further comprise a uracil glycosylase inhibitor (UGI) domain to mediate substitution of a U by a T, completing a C-to-T base editing event. In another example, the base editor can comprise a uracil stabilizing protein as described herein. In another example, a base editor can incorporate a translesion polymerase to improve the efficiency of C-to-G base editing, since a translesion polymerase can facilitate incorporation of a C opposite an abasic site (*i.e.*, resulting in incorporation of a G at the abasic site, completing the C-to-G base editing event).

A base editor comprising a cytidine deaminase as a domain can deaminate a target C in any polynucleotide, including DNA, RNA and DNA-RNA hybrids.

In some embodiments, a cytidine deaminase of a base editor comprises all or a portion (*e.g.*, a functional portion) of an apolipoprotein B mRNA editing complex (APOBEC) family deaminase. APOBEC is a family of evolutionarily conserved cytidine deaminases. Members of this family are C-to-U editing enzymes. The N-terminal domain of APOBEC like proteins is the catalytic domain, while the C-terminal domain is a pseudocatalytic domain. More specifically, the catalytic domain is a zinc dependent cytidine deaminase domain and is important for cytidine deamination. APOBEC family members include APOBEC1, APOBEC2, APOBEC3A, APOBEC3B, APOBEC3C, APOBEC3D (“APOBEC3E” now refers to this), APOBEC3F, APOBEC3G, APOBEC3H, APOBEC4, and Activation-induced (cytidine) deaminase.

Other exemplary deaminases that can be fused to Cas9 according to aspects of this disclosure are provided below. In embodiments, the deaminases are activation-induced deaminases (AID). It should be understood that, in some embodiments, the active domain of the respective sequence can be used, *e.g.*, the domain without a localizing signal (nuclear localization sequence, without nuclear export signal, cytoplasmic localizing signal).

Some aspects of the present disclosure are based on the recognition that modulating the deaminase domain catalytic activity of any of the fusion proteins or complexes described herein, for example by making point mutations in the deaminase domain, affect the

processivity of the fusion proteins (*e.g.*, base editors) or complexes. For example, mutations that reduce, but do not eliminate, the catalytic activity of a deaminase domain within a base editing fusion protein or complexes can make it less likely that the deaminase domain will catalyze the deamination of a residue adjacent to a target residue, thereby narrowing the deamination window. The ability to narrow the deamination window can prevent unwanted deamination of residues adjacent to specific target residues, which can reduce or prevent off-target effects.

In some embodiments, an APOBEC deaminase incorporated into a base editor can comprise one or more mutations selected from the group consisting of R33A, K34A, E63A, H102P, D104N, H121R, H122R, H122L, D124N; R126A, R126E, R118A, W90A, W90Y, and R132E of rAPOBEC1; D316R, D317R, R320A, R320E, R313A, W285A, W285Y, and R326E of hAPOBEC3G; and any alternative mutation at the corresponding position, or one or more corresponding mutations in another APOBEC deaminase. In some embodiments, an APOBEC deaminase incorporated into a base editor can comprise one or more combinations of mutations selected from K34A, H122L, and D124N (AALN); H102P and D104N (evoFERNY derived from FERNY); W90Y and R126E (YE1); W90Y and R132E (YE2); R126E and R132E (EE); W90Y, R126E, and R132E (YEE), or rAPOBEC1; and any alternative mutation at the corresponding positions, or one or more corresponding mutations in another APOBEC deaminase.

A number of modified cytidine deaminases are commercially available, including, but not limited to, SaBE3, SaKKH-BE3, VQR-BE3, EQR-BE3, VRER-BE3, YE1-BE3, EE-BE3, YE2-BE3, and YEE-BE3, which are available from Addgene (plasmids 85169, 85170, 85171, 85172, 85173, 85174, 85175, 85176, 85177). In some embodiments, a deaminase incorporated into a base editor comprises all or a portion (*e.g.*, a functional portion) of an APOBEC1 deaminase.

In some embodiments, the fusion proteins or complexes of the disclosure comprise one or more cytidine deaminase domains. In some embodiments, the cytidine deaminases provided herein are capable of deaminating cytosine or 5-methylcytosine to uracil or thymine. In some embodiments, the cytidine deaminases provided herein are capable of deaminating cytosine in DNA. The cytidine deaminase may be derived from any suitable organism. In some embodiments, the cytidine deaminase is a naturally-occurring cytidine deaminase that includes one or more mutations corresponding to any of the mutations provided herein. One of skill in the art will be able to identify the corresponding residue in any homologous protein, *e.g.*, by sequence alignment and determination of homologous

residues. Accordingly, one of skill in the art would be able to generate mutations in any naturally-occurring cytidine deaminase that corresponds to any of the mutations described herein. In some embodiments, the cytidine deaminase is from a prokaryote. In some embodiments, the cytidine deaminase is from a bacterium. In some embodiments, the cytidine deaminase is from a mammal (*e.g.*, human).

In some embodiments, the cytidine deaminase comprises an amino acid sequence that is at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 99.5% identical to any one of the cytidine deaminase amino acid sequences set forth herein. It should be appreciated that cytidine deaminases provided herein may include one or more mutations (*e.g.*, any of the mutations provided herein). Some embodiments provide a polynucleotide molecule encoding the cytidine deaminase nucleobase editor polypeptide of any previous aspect or as delineated herein. In some embodiments, the polynucleotide is codon optimized.

In embodiments, a fusion protein of the disclosure comprises two or more nucleic acid editing domains.

Details of C to T nucleobase editing proteins are described in International PCT Application No. PCT/US2016/058344 (WO2017/070632) and Komor, A.C., *et al.*, “Programmable editing of a target base in genomic DNA without double-stranded DNA cleavage” Nature 533, 420-424 (2016), the entire contents of which are hereby incorporated by reference. Further non-limiting examples of C to T nucleobase editing proteins are described in PCT Applications No. PCT/US2020/062428 and PCT/US2019/033848, the entire contents of which are hereby incorporated by reference.

Cytidine Adenosine Base Editors (CABEs)

In some embodiments, a base editor described herein comprises an adenosine deaminase variant that has increased cytidine deaminase activity. Such base editors may be referred to as “cytidine adenosine base editors (CABEs)” or “cytosine base editors derived from TadA* (CBE-Ts),” and their corresponding deaminase domains may be referred to as “TadA* acting on DNA cytosine (T_{AD}C)” domains or TadA-derived cytidine deaminases (TadA-CD). Base editors containing adenosine deaminase variants having both cytidine deaminase and adenosine deaminase activity (*i.e.*, TadA-Dual deaminases) may be referred to as TadA-based dual editors (TadDE). In some instances, an adenosine deaminase variant has both adenine and cytosine deaminase activity (*i.e.*, is a dual deaminase). In some

embodiments, the adenosine deaminase variants deaminate adenine and cytosine in DNA. In some embodiments, the adenosine deaminase variants deaminate adenine and cytosine in single-stranded DNA. In some embodiments, the adenosine deaminase variants deaminate adenine and cytosine in RNA. In some embodiments, the adenosine deaminase variant

5 predominantly deaminates cytosine in DNA and/or RNA (e.g., greater than 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 99% of all deaminations catalyzed by the adenosine deaminase variant, or the number of cytosine deaminations catalyzed by the variant is about or at least about 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, 10-fold, 25-fold, 50-fold, 75-fold, 100-fold, 500-fold, or 1,000-fold greater than the number adenine

10 deaminations catalyzed by the variant). In some embodiments, the adenosine deaminase variant has approximately equal cytosine and adenosine deaminase activity (e.g., the two activities are within about 10% or 20% of each other). In some embodiments, the adenosine deaminase variant has predominantly cytosine deaminase activity, and little, if any, adenosine deaminase activity. In some embodiments, the adenosine deaminase variant has cytosine

15 deaminase activity, and no significant or no detectable adenosine deaminase activity. In some embodiments, the target polynucleotide is present in a cell *in vitro* or *in vivo*. In some embodiments, the cell is a bacteria, yeast, fungi, insect, plant, or mammalian cell. Examples of adenosine deaminase variants having increased cytidine deaminase activity include those described in International Patent Application Publications No. WO 2024/040083 and WO

20 2022/204574, the disclosures of which are hereby incorporated by reference in their entireties for all purposes.

In some embodiments, the CAGE comprises a bacterial TadA deaminase variant (e.g., ecTadA). In some embodiments, the CAGE comprises a truncated TadA deaminase variant. In some embodiments, the CAGE comprises a fragment of a TadA deaminase variant. In

25 some embodiments, the CAGE comprises a TadA*8.20 variant.

In some embodiments, an adenosine deaminase variant of the disclosure is a TadA adenosine deaminase comprising one or more alterations that increase cytosine deaminase activity (e.g., at least about 10-fold, 20-fold, 30-fold, 40-fold, 50-fold, 60-fold, 70-fold or more increase) while maintaining adenosine deaminase activity (e.g., at least about 30%,

30 40%, 50% or more of the activity of a reference adenosine deaminase (e.g., TadA*8.20 or TadA*8.19)). In some instances, the adenosine deaminase variant comprises one or more alterations that increase cytosine deaminase activity (e.g., at least about 10-fold, 20-fold, 30-fold, 40-fold, 50-fold, 60-fold, 70-fold or more increase) relative to the activity of a reference adenosine deaminase and comprise undetectable adenosine deaminase activity or adenosine

deaminase activity that is less than 30%, 20%, 10%, or 5% of that of a reference adenosine deaminase. In some embodiments, the reference adenosine deaminase is TadA*8.20 or TadA*8.19.

In some embodiments, the adenosine deaminase variant is an adenosine deaminase comprising two or more alterations at an amino acid position selected from the group consisting of 2, 4, 6, 8, 13, 17, 23, 27, 29, 30, 47, 48, 49, 67, 76, 77, 82, 84, 96, 100, 107, 112, 114, 115, 118, 119, 122, 127, 142, 143, 147, 149, 158, 159, 162, 165, 166, and 167, of an amino acid sequence having at least about 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% or greater identity to SEQ ID NO: 1, or a corresponding alteration in another deaminase. I

In some embodiments, the adenosine deaminase variant is an adenosine deaminase comprising one or more alterations selected from the group consisting of S2H, V4K, V4S, V4T, V4Y, F6G, F6H, F6Y, H8Q, R13G, T17A, T17W, R23Q, E27C, E27G, E27H, E27K, E27Q, E27S, E27G, P29A, P29G, P29K, V30F, V30I, R47G, R47S, A48G, I49K, I49M, I49N, I49Q, I49T, G67W, I76H, I76R, I76W, Y76H, Y76R, Y76W, F84A, F84M, H96N, G100A, G100K, T111H, G112H, A114C, G115M, M118L, H122G, H122R, H122T, N127I, N127K, N127P, A142E, R147H, A158V, Q159S, A162C, A162N, A162Q, and S165P of an amino acid sequence having at least about 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% or greater identity to SEQ ID NO: 1, or a corresponding alteration in another deaminase.

In some embodiments, the adenosine deaminase variant is an adenosine deaminase comprising an amino acid alteration or combination of amino acid alterations selected from those listed in any of **Tables 6A-6F**.

The residue identity of exemplary adenosine deaminase variants that are capable of deaminating adenine and/or cytidine in a target polynucleotide (*e.g.*, DNA) is provided in **Tables 6A-6F** below. Further examples of adenosine deaminase variants include the following variants of 1.17 (see **Table 6A**): 1.17+E27H; 1.17+E27K; 1.17+E27S; 1.17+E27S+I49K; 1.17+E27G; 1.17+I49N; 1.17+E27G+I49N; and 1.17+E27Q. In some embodiments, any of the amino acid alterations provided herein are substituted with a conservative amino acid. Additional mutations known in the art can be further added to any of the adenosine deaminase variants provided herein.

In some embodiments, the base editor systems comprising a CBE provided herein have at least about a 30%, 40%, 50%, 60%, 70% or more C to T editing activity in a target polynucleotide (*e.g.*, DNA). In some embodiments, a base editor system comprising a CBE as provided herein has an increased C to T base editing activity (*e.g.*, increased at least about

30-fold, 40-fold, 50-fold, 60-fold, 70-fold or more) relative to a reference base editor system comprising a reference adenosine deaminase (*e.g.*, TadA*8.20 or TadA*8.19).

5 **Table 6A. Adenosine Deaminase Variants. Mutations are indicated with reference to TadA*8.20. “S” indicates “Surface,” and “NAS” indicates “Near Active Site.”**

location in structure	N/A	S h1	S h1	S h1	NAS	NAS	NAS	NAS		S	
Amino Acid No. (*START Met is AA#1)	2	8	13	17	27	47	48	49	67	76	77
TadA*8.20	S	H	R	T	E	R	A	I	G	Y	D
TadA*8.19										I	
1.1					H					I	
1.2					H			K		I	
1.3					S			K		I	
1.4					S			K		I	
1.5					K						
1.6					K						
1.7					H					I	
1.8					S			K	W		
1.9								T	W		
1.10					C					I	
1.11			G		Q						
1.12				A	H			M		I	
1.13								Q		I	
1.14	H							K		I	
1.15						S					
1.16		Q						Q		I	
1.17				A			G				
1.18					G						
1.19					G			N			
1.20					G						G

Table 6A (continued). Adenosine Deaminase Variants. Mutations are indicated with reference to TadA*8.20. “I” indicates “Internal,” “S” indicates “Surface,” and “NAS” indicates “Near Active Site.”

location in structure	I	NAS		NAS	S		S	S	S		S	
Amino Acid No. (*START Met is AA#1)	82	84	96	107	112	115	118	119	127	142	162	165
TadA*8.20	S	F	H	R	G	G	M	D	N	A	A	S
TadA*8.19												
1.1		M										
1.2												
1.3												

location in structure	I	NAS		NAS	S		S	S	S		S	
Amino Acid No. (*START Met is AA#1)	82	84	96	107	112	115	118	119	127	142	162	165
TadA*8.20	S	F	H	R	G	G	M	D	N	A	A	S
TadA*8.19												
1.4											N	
1.5												
1.6								N				
1.7												
1.8												
1.9			N									
1.10								N				
1.11									K			
1.12							L					
1.13						M						
1.14					H							
1.15				C								
1.16												
1.17	T									E		
1.18												
1.19												
1.20												P

Table 6B. Adenosine deaminase variants. Mutations are indicated with reference to TadA*8.20.

Position No.	27	29	30	49	82	84	107	112	115	142
TadA*8.20	E	P	V	I	S	F	R	G	G	A
Alterations Evaluated	G/S/H	G/A/K	I/L/F	K	T	L/A	C	H	M	E
S1.1	S			K	T					
S1.2	S			K	T		C			
S1.3	S			K	T			H		
S1.4	S			K	T				M	
S1.5	S			K	T					E
S1.6	S			K	T		C	H		
S1.7	S			K	T		C		M	
S1.8	S			K	T		C			E
S1.9	S			K	T			H		E
S1.10	S			K	T				M	E
S1.11	S			K	T		C	H	M	E
S1.12	S		I	K	T					
S1.13	S		I	K	T		C			
S1.14	S		I	K	T			H		

Position No.	27	29	30	49	82	84	107	112	115	142
TadA*8.20	E	P	V	I	S	F	R	G	G	A
Alterations Evaluated	G/S/H	G/A/K	I/L/F	K	T	L/A	C	H	M	E
S1.15	S		I	K	T				M	
S1.16	S		I	K	T					E
S1.17	S		I	K	T		C	H		
S1.18	S		I	K	T		C		M	
S1.19	S		I	K	T		C			E
S1.20	S		I	K	T			H		E
S1.21	S		I	K	T				M	E
S1.22	S		I	K	T		C	H	M	E
S1.23	S		L	K	T					
S1.24	S		L	K	T		C			
S1.25	S		L	K	T			H		
S1.26	S		L	K	T				M	
S1.27	S		L	K	T					E
S1.28	S		L	K	T		C	H		
S1.29	S		L	K	T		C		M	
S1.30	S		L	K	T		C			E
S1.31	S		L	K	T			H		E
S1.32	S		L	K	T				M	E
S1.33	S		L	K	T		C	H	M	E
S1.34	S		F	K	T	A				
S1.35	S		F	K	T	A	C			
S1.36	S		F	K	T	A		H		
S1.37	S		F	K	T	A			M	
S1.38	S		F	K	T	A				E
S1.39	S		F	K	T	A	C	H		
S1.40	S		F	K	T	A	C		M	
S1.41	S		F	K	T	A	C			E
S1.42	S		F	K	T	A		H		E
S1.43	S		F	K	T	A			M	E
S1.44	S		F	K	T	A	C	H	M	E
S1.45	S			K	T	L				
S1.46	S			K	T	L	C			
S1.47	S			K	T	L		H		
S1.48	S			K	T	L			M	
S1.49	S			K	T	L				E
S1.50	S			K	T	L	C	H		
S1.51	S			K	T	L	C		M	
S1.52	S			K	T	L	C			E
S1.53	S			K	T	L		H		E
S1.54	S			K	T	L			M	E
S1.55	S			K	T	L	C	H	M	E
S1.56	S		I	K	T	L				

Position No.	27	29	30	49	82	84	107	112	115	142
TadA*8.20	E	P	V	I	S	F	R	G	G	A
Alterations Evaluated	G/S/H	G/A/K	I/L/F	K	T	L/A	C	H	M	E
S1.57	S		I	K	T	L	C			
S1.58	S		I	K	T	L		H		
S1.59	S		I	K	T	L			M	
S1.60	S		I	K	T	L				E
S1.61	S		I	K	T	L	C	H		
S1.62	S		I	K	T	L	C		M	
S1.63	S		I	K	T	L	C			E
S1.64	S		I	K	T	L		H		E
S1.65	S		I	K	T	L			M	E
S1.66	S		I	K	T	L	C	H	M	E
S1.67	S	G		K	T					
S1.68	S	G		K	T		C			
S1.69	S	G		K	T			H		
S1.70	S	G		K	T				M	
S1.71	S	G		K	T					E
S1.72	S	G		K	T		C	H		
S1.73	S	G		K	T		C		M	
S1.74	S	G		K	T		C			E
S1.75	S	G		K	T			H		E
S1.76	S	G		K	T				M	E
S1.77	S	G		K	T		C	H	M	E
S1.78		G		K	T					
S1.79		G		K	T		C			
S1.80		G		K	T			H		
S1.81		G		K	T				M	
S1.82		G		K	T					E
S1.83		G		K	T		C	H		
S1.84		G		K	T		C		M	
S1.85		G		K	T		C			E
S1.86		G		K	T			H		E
S1.87		G		K	T				M	E
S1.88		G		K	T		C	H	M	E
S1.89		K		K	T					
S1.90		K		K	T		C			
S1.91		K		K	T			H		
S1.92		K		K	T				M	
S1.93		K		K	T					E
S1.94		K		K	T		C	H		
S1.95		K		K	T		C		M	
S1.96		K		K	T		C			E
S1.97		K		K	T			H		E
S1.98		K		K	T				M	E

Position No.	27	29	30	49	82	84	107	112	115	142
TadA*8.20	E	P	V	I	S	F	R	G	G	A
Alterations Evaluated	G/S/H	G/A/K	I/L/F	K	T	L/A	C	H	M	E
S1.99		K		K	T		C	H	M	E
S1.100		K	I	K	T					
S1.101		K	I	K	T		C			
S1.102		K	I	K	T			H		
S1.103		K	I	K	T				M	
S1.104		K	I	K	T					E
S1.105		K	I	K	T		C	H		
S1.106		K	I	K	T		C		M	
S1.107		K	I	K	T		C			E
S1.108		K	I	K	T			H		E
S1.109		K	I	K	T				M	E
S1.110		K	I	K	T		C	H	M	E
S1.111		K		K	T	L				
S1.112		K		K	T	L	C			
S1.113		K		K	T	L		H		
S1.114		K		K	T	L			M	
S1.115		K		K	T	L				E
S1.116		K		K	T	L	C	H		
S1.117		K		K	T	L	C		M	
S1.118		K		K	T	L	C			E
S1.119		K		K	T	L		H		E
S1.120		K		K	T	L			M	E
S1.121		K		K	T	L	C	H	M	E
S1.122		K	I	K	T	L				
S1.123		K	I	K	T	L	C			
S1.124		K	I	K	T	L		H		
S1.125		K	I	K	T	L			M	
S1.126		K	I	K	T	L				E
S1.127		K	I	K	T	L	C	H		
S1.128		K	I	K	T	L	C		M	
S1.129		K	I	K	T	L	C			E
S1.130		K	I	K	T	L		H		E
S1.131		K	I	K	T	L			M	E
S1.132		K	I	K	T	L	C	H	M	E
S1.133	G			K	T					
S1.134	G			K	T		C			
S1.135	G			K	T			H		
S1.136	G			K	T				M	
S1.137	G			K	T					E
S1.138	G			K	T		C	H		
S1.139	G			K	T		C		M	
S1.140	G			K	T		C			E

Position No.	27	29	30	49	82	84	107	112	115	142
TadA*8.20	E	P	V	I	S	F	R	G	G	A
Alterations Evaluated	G/S/H	G/A/K	I/L/F	K	T	L/A	C	H	M	E
S1.141	G			K	T			H		E
S1.142	G			K	T				M	E
S1.143	G			K	T		C	H	M	E
S1.144	H			K	T					
S1.145	H			K	T		C			
S1.146	H			K	T			H		
S1.147	H			K	T				M	
S1.148	H			K	T					E
S1.149	H			K	T		C	H		
S1.150	H			K	T		C		M	
S1.151	H			K	T		C			E
S1.152	H			K	T			H		E
S1.153	H			K	T				M	E
S1.154	H			K	T		C	H	M	E
S1.155	S				T					
S1.156	S				T		C			
S1.157	S				T			H		
S1.158	S				T				M	
S1.159	S				T					E
S1.160	S				T		C	H		
S1.161	S				T		C		M	
S1.162	S				T		C			E
S1.163	S				T			H		E
S1.164	S				T				M	E
S1.165	S				T		C	H	M	E
S1.166		A			T					
S1.167		A			T		C			
S1.168		A			T			H		
S1.169		A			T				M	
S1.170		A			T					E
S1.171		A			T		C	H		
S1.172		A			T		C		M	
S1.173		A			T		C			E
S1.174		A			T			H		E
S1.175		A			T				M	E
S1.176		A			T		C	H	M	E
S1.177	S		I		T					
S1.178	S		I		T		C			
S1.179	S		I		T			H		
S1.180	S		I		T				M	
S1.181	S		I		T					E
S1.182	S		I		T		C	H		

Position No.	27	29	30	49	82	84	107	112	115	142
TadA*8.20	E	P	V	I	S	F	R	G	G	A
Alterations Evaluated	G/S/H	G/A/K	I/L/F	K	T	L/A	C	H	M	E
S1.183	S		I		T		C		M	
S1.184	S		I		T		C			E
S1.185	S		I		T			H		E
S1.186	S		I		T				M	E
S1.187	S		I		T		C	H	M	E
S1.188		A	I		T	L				
S1.189		A	I		T	L	C			
S1.190		A	I		T	L		H		
S1.191		A	I		T	L			M	
S1.192		A	I		T	L				E
S1.193		A	I		T	L	C	H		
S1.194		A	I		T	L	C		M	
S1.195		A	I		T	L	C			E
S1.196		A	I		T	L		H		E
S1.197		A	I		T	L			M	E
S1.198		A	I		T	L	C	H	M	E
S1.199	S	A	L	K	T	L	C	H	M	E

Table 6C. Adenosine deaminase variants. Mutations are indicated with reference to variant 1.2 (Table 6A) .

		Residue identity (START Met is amino acid #1)								
Variant Name	Alternative Variant Names	4	6	17	23	76	77	100	101	104
Reference	1.2 (see Table 6A)	V	F	T	R	I	D	G	T	A
TadAC2.1	pDKL-135; 2.1	K								C
TadAC2.2	pDKL-136; 2.2	K					G			
TadAC2.3	pDKL-137; 2.3		Y					A		
TadAC2.4	pDKL-138; 2.4	T				R				
TadAC2.5	pDKL-139; 2.5		Y			W				
TadAC2.6	pDKL-140; 2.6		Y							
TadAC2.7	pDKL-141; 2.7		Y							C
TadAC2.8	pDKL-142; 2.8		Y							
TadAC2.9	pDKL-143; 2.9	K				W				
TadAC2.10	pDKL-144; 2.10		G			R		K		
TadAC2.11	pDKL-145; 2.11		H							
TadAC2.12	pDKL-146; 2.12									C
TadAC2.13	pDKL-147; 2.13		Y			H				
TadAC2.14	pDKL-148; 2.14									

		Residue identity (START Met is amino acid #1)								
Variant Name	Alternative Variant Names	4	6	17	23	76	77	100	101	104
Reference	1.2 (see Table 6A)	V	F	T	R	I	D	G	T	A
TadAC2.15	pDKL-149; 2.15				Q	R				
TadAC2.16	pDKL-150; 2.16					H				
TadAC2.17	pDKL-151; 2.17		Y						H	
TadAC2.18	pDKL-152; 2.18					W				
TadAC2.19	pDKL-153; 2.19								H	
TadAC2.20	pDKL-154; 2.20									
TadAC2.21	pDKL-155; 2.21		Y			R				
TadAC2.22	pDKL-156; 2.22			W		H				
TadAC2.23	pDKL-157; 2.23	S				Y				
TadAC2.24	pDKL-158; 2.24									

Table 6C. (CONTINUED)

		Residue identity (START Met is amino acid #1)								
Variant Name	Alternative Variant Names	119	122	127	143	144	145	148	149	166
Reference	1.2 (see Table 6A)	D	H	N	A	R	A	Q	A	T
TadAC2.1	pDKL-135; 2.1									
TadAC2.2	pDKL-136; 2.2									
TadAC2.3	pDKL-137; 2.3		R							
TadAC2.4	pDKL-138; 2.4		G							
TadAC2.5	pDKL-139; 2.5									
TadAC2.6	pDKL-140; 2.6	N								
TadAC2.7	pDKL-141; 2.7									
TadAC2.8	pDKL-142; 2.8									
TadAC2.9	pDKL-143; 2.9		T							
TadAC2.10	pDKL-144; 2.10									
TadAC2.11	pDKL-145; 2.11		N							
TadAC2.12	pDKL-146; 2.12									
TadAC2.13	pDKL-147; 2.13		R							I
TadAC2.14	pDKL-148; 2.14			P						
TadAC2.15	pDKL-149; 2.15									
TadAC2.16	pDKL-150; 2.16		R			V				
TadAC2.17	pDKL-151; 2.17									
TadAC2.18	pDKL-152; 2.18									
TadAC2.19	pDKL-153; 2.19		G					C		

		Residue identity (START Met is amino acid #1)								
Variant Name	Alternative Variant Names	1 1 9	1 2 2	1 2 7	1 4 3	1 4 7	1 5 8	1 5 9	1 6 2	16 6
Reference	1.2 (see Table 6A)	D	H	N	A	R	A	Q	A	T
TadAC2.20	pDKL-154; 2.20				E					
TadAC2.21	pDKL-155; 2.21									
TadAC2.22	pDKL-156; 2.22		G				V			
TadAC2.23	pDKL-157; 2.23				E			S		
TadAC2.24	pDKL-158; 2.24			I					Q	

Table 6D. Adenosine deaminase variants. Mutations are indicated with reference to TadA*8.20.

AA Positions	6	27	49	76	77	82	107	112	114	115	119	122	127	142	143
TadA*8.20	F	E	I	Y	D	S	R	G	A	G	D	H	N	A	A
S1.154	F	H	K	Y	D	T	C	H		M				E	
Alterations from Table 6C	Y			W	G				C		N	G	P		E
S2.1	Y	H	K	W		T	C	H		M				E	
S2.2	Y	H	K		G	T	C	H		M				E	
S2.3	Y	H	K			T	C	H	C	M				E	
S2.4	Y	H	K			T	C	H		M	N			E	
S2.5	Y	H	K			T	C	H		M		G		E	
S2.6	Y	H	K			T	C	H		M			P	E	
S2.7	Y	H	K			T	C	H		M				E	E
S2.8	Y	H	K			T	C	H		M				A	E
S2.9	Y	H	K	W	G	T	C	H		M				E	
S2.10	Y	H	K	W		T	C	H	C	M				E	
S2.11	Y	H	K	W		T	C	H		M	N			E	
S2.12	Y	H	K	W		T	C	H		M		G		E	
S2.13	Y	H	K	W		T	C	H		M			P	E	
S2.14	Y	H	K	W		T	C	H		M				E	E
S2.15	Y	H	K	W		T	C	H		M				A	E
S2.16	Y	H	K		G	T	C	H	C	M				E	
S2.17	Y	H	K		G	T	C	H		M	N			E	
S2.18	Y	H	K		G	T	C	H		M		G		E	
S2.19	Y	H	K		G	T	C	H		M			P	E	

AA Positions	6	27	49	76	77	82	107	112	114	115	119	122	127	142	143
TadA*8.20	F	E	I	Y	D	S	R	G	A	G	D	H	N	A	A
S2.20	Y	H	K		G	T	C	H		M				E	E
S2.21	Y	H	K		G	T	C	H		M				A	E
S2.22	Y	H	K			T	C	H	C	M	N			E	
S2.23	Y	H	K			T	C	H	C	M		G		E	
S2.24	Y	H	K			T	C	H	C	M			P	E	
S2.25	Y	H	K			T	C	H		M	N	G		E	
S2.26	Y	H	K			T	C	H		M	N		P	E	
S2.27	Y	H	K			T	C	H		M		G	P	E	
S2.28	Y	H	K	W	G	T	C	H	C	M				E	
S2.29	Y	H	K	W	G	T	C	H		M	N			E	
S2.30	Y	H	K	W	G	T	C	H		M		G		E	
S2.31	Y	H	K	W	G	T	C	H		M			P	E	
S2.32	Y	H	K	W	G	T	C	H		M				E	E
S2.33	Y	H	K	W	G	T	C	H		M				A	E
S2.34	Y	H	K	W		T	C	H	C	M	N			E	
S2.35	Y	H	K	W		T	C	H	C	M		G		E	
S2.36	Y	H	K	W		T	C	H	C	M			P	E	
S2.37	Y	H	K	W		T	C	H	C	M				E	E
S2.38	Y	H	K	W		T	C	H	C	M				A	E
S2.39	Y	H	K	W		T	C	H		M	N	G		E	
S2.40	Y	H	K	W		T	C	H		M	N		P	E	
S2.41	Y	H	K	W		T	C	H		M		G	P	E	
S2.42	Y	H	K	W		T	C	H	C	M	N	G		E	
S2.43	Y	H	K	W		T	C	H	C	M	N		P	E	
S2.44	Y	H	K	W		T	C	H	C	M		G	P	E	
S2.45	Y	H	K	W	G	T	C	H	C	M	N			E	
S2.46	Y	H	K	W	G	T	C	H	C	M		G		E	
S2.47	Y	H	K	W	G	T	C	H	C	M			P	E	
S2.48	Y	H	K	W	G	T	C	H	C	M				E	E
S2.49	Y	H	K	W	G	T	C	H	C	M				A	E
S2.50	Y	H	K	W	G	T	C	H	C	M	N	G		E	
S2.51	Y	H	K	W	G	T	C	H	C	M	N		P	E	
S2.52	Y	H	K	W	G	T	C	H	C	M		G	P	E	
S2.53	Y	H	K	W		T	C	H	C	M	N	G	P	E	E
S2.54	Y	H	K	W		T	C	H	C	M	N	G	P	A	E
S2.55	Y	H	K	W	G	T	C	H	C	M	N	G	P	E	E

AA Positions	6	27	49	76	77	82	107	112	114	115	119	122	127	142	143
TadA*8.20	F	E	I	Y	D	S	R	G	A	G	D	H	N	A	A
S2.56	Y	H	K	W	G	T	C	H	C	M	N	G	P	A	E

Table 6E. Hybrid constructs. Mutations are indicated with reference to TadA*7.10.

	TadA amino acid substitutions											
	76	82	109	111	119	122	123	147	149	154	166	167
TadA*7.10	I	V	A	T	D	H	Y	Y	F	Q	T	D
TadA*8e			S	R	N	N		D	Y		I	N
TadA*8.20	Y	S					H	R		R		
TadA*8.17		S								R		
pNMG-B878	Y	S					H	D		R		
pNMG-B879	Y	S					H	R	Y	R		
pNMG-B880	Y	S					H	R		R	I	
pNMG-B881	Y	S					H	R		R		N
pNMG-B882	Y	S					H	D	Y	R	I	N
pNMG-B883	Y	S		R	N		H	R		R		
pNMG-B884	Y	S	S	R	N	N	H	R		R		
pNMG-B885	Y	S	S				H	R		R		
pNMG-B886	Y	S		R			H	R		R		
pNMG-B887	Y	S			N		H	R		R		
pNMG-B888	Y	S				N	H	R		R		
pNMG-B889	Y	S	S	R			H	R		R		
pNMG-B890	Y	S			N	N	H	R		R		
pNMG-B891	Y	S	S	R	N	N	H	D	Y	R	I	N

Table 6F. Base editor variants. Mutations are indicated with reference to TadA*8.19/8.20.

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AA positions:	17	27	48	49	76	82	84	118	142	147	149	166	167
ABE8.19m/8.20m	T	E	A	I	Y/I	S	F	M	A	Y	F	T	D
1.1 + 8e(B879)		H			I		M				Y		
1.2 + 8e(B879)		H		K	I						Y		
1.12 + 8e(B879)	A	H		M	I			L			Y		
1.17 + 8e(B879)	A		G			T			E		Y		
1.18 + 8e(B879)		G									Y		
1.19 + 8e(B879)		G		N							Y		
1.1 + 8e(B882)		H			I		M			D	Y	I	N
1.2 + 8e(B882)		H		K	I					D	Y	I	N
1.12 + 8e(B882)	A	H		M	I			L		D	Y	I	N
1.17 + 8e(B882)	A		G			T			E	D	Y	I	N
1.18 + 8e(B882)		G								D	Y	I	N

AA positions:	17	27	48	49	76	82	84	118	142	147	149	166	167
ABE8.19m/8.20m	T	E	A	I	Y/I	S	F	M	A	Y	F	T	D
1.19 + 8e(B882)		G		N						D	Y	I	N

A TadA-derived cytidine deaminase (e.g., TadA-CD), according to certain embodiments, comprises an amino acid sequence that is at least 80% identical, at least 85% identical, at least 90% identical, at least 95% identical, at least 98% identical, at least 99% identical, and at least 99.5% identical to the amino acid sequence of SEQ ID NO: 3594, wherein residue 27 of SEQ ID NO: 3594 is any amino acid expect for E (glutamic acid). TadA-CDs with other sequence homologies are also possible. For example, in certain embodiments, the TadA-derived cytidine deaminase (e.g., TadA-CD) comprises an amino acid sequence that is at least 80% identical, at least 85% identical, at least 90% identical, at least 95% identical, at least 98% identical, at least 99% identical, and at least 99.5% identical to the amino acid sequence of SEQ ID NO: 3594, wherein residue 28 of SEQ ID NO: 3594 is any amino acid expect for V (valine). In another exemplary embodiment, the TadA-derived cytidine deaminase is at least 80% identical, at least 85% identical, at least 90% identical, at least 95% identical, at least 98% identical, at least 99% identical, and at least 99.5% identical to the amino acid sequence of SEQ ID NO: 3594, wherein residue 96 of SEQ ID NO: 3594 is any amino acid expect for H (histidine). In another exemplary embodiment, the TadA-derived cytidine deaminase is at least 80% identical, at least 85% identical, at least 90% identical, at least 95% identical, at least 98% identical, at least 99% identical, and at least 99.5% identical to the amino acid sequence of SEQ ID NO: 3594, wherein residue 26 of SEQ ID NO: 3594 is any amino acid expect for R (arginine). In various embodiments, the TadA-derived cytidine deaminase comprises an alteration at one or more of positions 26, 27, 28, 48, 73, or 96 compared to SEQ ID NO: 3594.

As will be appreciated by those of skill in the art, TadA-derived cytidine deaminases (e.g., TadA-CD) may comprise a plurality of mutations relative to the parent adenosine deaminase (e.g., TadA-8e). In some embodiments, the deaminase of the instant application (e.g., TadA-CD) comprises mutations at residues E27, V28, and H96. In some embodiments, the disclosed deaminase further comprises at least one mutation at a residue selected from R26, M61, Y73, I76, M151, Q154, and A158, in the amino acid sequence of SEQ ID NO: 3594, or corresponding mutations in a homologous adenosine deaminase.

In some embodiments, the deaminase comprises at least one mutation selected from E27A, E27K, V28G, V28A, and H96N, and further comprises at least one mutation at a

residue selected from R26G, M61I, Y73H, Y73S, Y73C, I76F, M151I, Q154R, Q154H, and A158S, in the amino acid sequence of SEQ ID NO: 3594, or a corresponding mutation in a homologous adenosine deaminase. Other mutations are also possible. For example, in certain embodiments, the TadA-CD enzyme comprises mutations selected from E27A, V28G, and H96N, and further comprises at least one mutation selected from R26G, M61I, Y73H, Y73S, Y73C, I76F, M151I, Q154R, Q154H, and A158S, in the amino acid sequence of SEQ ID NO: 3594, or corresponding mutations in a homologous adenosine deaminase.

Other exemplary embodiments may include (1) deaminases comprising mutations E27K, V28G, and H96N, and further comprising at least one mutation selected from R26G, M61I, Y73H, Y73S, Y73C, I76F, M151I, Q154R, Q154H, and A158S, in the amino acid sequence of SEQ ID NO: 3594 or corresponding mutations in a homologous adenosine deaminase; (2) deaminases comprising mutations E27A, V28A, and H96N, and further comprising at least one mutation selected from R26G, M61I, Y73H, Y73S, Y73C, I76F, M151I, Q154R, Q154H, and A158S, in the amino acid sequence of SEQ ID NO: 3594, or corresponding mutations in a homologous adenosine deaminase; (3) deaminases comprising mutations E27K, V28A, and H96N, and further comprising at least one mutation selected from R26G, M61I, Y73H, Y73S, Y73C, I76F, M151I, Q154R, Q154H, and A158S, in the amino acid sequence of SEQ ID NO: 3594, or corresponding mutations in a homologous adenosine deaminase.

In some embodiments, the TadA-derived cytidine deaminases (TadA-CD) comprise at least two mutations at residues selected from R26, M61, Y73, I76, M151, Q154, and A158 (relative to a reference adenosine deaminase). In other embodiments, the TadA-CD comprises at least two mutations at residues selected from R26G, M61I, Y73H, I76F, M151I, Q154H, Q154R, and A158S.

In some embodiments, the addition of a V106W mutation improves the selectivity by suppressing A deamination to a greater extent than C deamination.

In some embodiments, a TadA-based dual editor comprises an adenosine deaminase variant comprising one, two, three, four, or five mutations selected from R26G, V28A, A48R, Y73S, and H96N (e.g., SEQ ID NO: 3600).

As such, in some embodiments, provided herein are deaminases that comprise mutations at residues R26, V28, A48, and Y73 in the amino acid sequence of SEQ ID NO: 3594, or corresponding mutations in a homologous adenosine deaminase. Further provided herein are deaminases that comprise mutations at residues R26, E27, V28, A48, and Y73 (e.g., further comprise a mutation at E27) in the amino acid sequence of SEQ ID NO: 3594.

In particular embodiments, these deaminases comprise the mutations R26G, V28A, A48R, Y73S, and H96N. In some embodiments, these deaminases comprise the mutations R26G, V28G, A48R, and Y73C.

TadA-CD variants may comprise at least one mutation selected from R26G, E27A, V28G, I76F, H96N, and M151I (e.g., TadA-CDa, SEQ ID NO: 3595); R26G, E27A, V28G, I76F, H96N, and A158S (e.g., TadA-CDb, SEQ ID NO: 3596); R26G, E27A, V28G, I76F, H96N, Q154R, and A158S (e.g., TadA-CDc, SEQ ID NO: 3597); E27A, V28G, Y73H, H96N, Q154H, and A158S (e.g., TadA-CDd, SEQ ID NO: 3598); R26G, V28A, A48R, Y73S, and H96N (e.g., TadA-CDe, SEQ ID NO: 3599); V28A, A48R, and Y73S (e.g., TadA-CDf, SEQ ID NO: 3600), and R26G, V28G, A48R, and Y73C (e.g., TadA-CDg, SEQ ID NO: 3601).

In some preferred embodiments, the deaminase comprises the mutations R26G, E27A, V28G, I76F, H96N, and A158S (e.g., TadA-CDa, SEQ ID NO: 3595), R26G, E27A, V28G, I76F, H96N, Q154R, and A158S (e.g., TadA-CDb, SEQ ID NO: 3596), R26G, E27A, V28G, I76F, H96N, and M151I (e.g., TadA-CDc, SEQ ID NO: 3597), E27K, V28A, M61I, and H96N (e.g., TadA-CDd, SEQ ID NO: 3598), E27A, V28G, Y73H, H96N, Q154H, and A158S (e.g., TadA-CDe, SEQ ID NO: 3599), R26G, V28A, A48R, Y73S, and H96N (e.g., TadA-CDf, SEQ ID NO: 3600), and R26G, V28G, A48R, and Y73C (e.g., TadA-CDg, SEQ ID NO: 3601).

In some embodiments, the TadA-CD variants described above and herein may also comprises a V106W mutation.

In some embodiments, the TadA-CD variants comprise at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or at least 99.5% to any of the amino acid sequences of SEQ ID NOs: 3594-3601.

In some embodiments, the evolved TadA-Dual deaminase comprises the mutations R26G, V28A, N46I, A48R, Y73P, and H96N (TadA-CD-1, SEQ ID NO: 3602) relative to the amino acid sequence of SEQ ID NO: 3594. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations R26G, V28A, N46T, A48R, Y73P, and H96N (TadA-CD-2, SEQ ID NO: 3603) relative to the amino acid sequence of SEQ ID NO: 3594. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations R26G, V28A, N46T, A48R, Y73S, and H96N (TadA-CD-3, SEQ ID NO: 3604) relative to the amino acid sequence of SEQ ID NO: 3594. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations R26G, V28A, N46V, A48R, Y73S, and H96N (TadA-CD-4, SEQ ID NO: 3605) relative to the amino acid sequence of SEQ ID NO: 3594. In some

embodiments, the evolved TadA-Dual deaminase comprises the mutations R26G, V28A, N46V, A48R, Y73P, and H96N (TadA-CD-5, SEQ ID NO: 3606) relative to the amino acid sequence of SEQ ID NO: 3594. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations R26G, V28A, N46L, A48R, Y73P, and H96N (TadA-CD-6, SEQ ID NO: 3607) relative to the amino acid sequence of SEQ ID NO: 3594. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations V28A, N46L, A48P, and Y73P (TadA-CD-7, SEQ ID NO: 3608) relative to the amino acid sequence of SEQ ID NO: 3594. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations V28A, N46C, A48P, and Y73P (TadA-CD-8, SEQ ID NO: 3609) relative to the amino acid sequence of SEQ ID NO: 3594. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations R26G, V28A, N46V, A48R, Y73P, and H96N (TadA-CD-9, SEQ ID NO: 3610) relative to the amino acid sequence of SEQ ID NO: 3594. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations R26G, V28A, N46V, A48R, Q71H, Y73P, and H96N (TadA-CD-10, SEQ ID NO: 3611) relative to the amino acid sequence of SEQ ID NO: 3594. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations R26G, V28A, N46L, A48R, Y73P, and H96N (TadA-CD-11, SEQ ID NO: 3612) relative to the amino acid sequence of SEQ ID NO: 3594. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations R26G, V28A, N46C, A48R, Y73P, and H96N (TadA-CD-12, SEQ ID NO: 3613) relative to the amino acid sequence of SEQ ID NO: 3594. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations R26G, V28A, N46C, A48R, Y73P, H96N, and A162V (TadA-CD-13, SEQ ID NO: 3614) relative to the amino acid sequence of SEQ ID NO: 3594.

In some embodiments, the evolved TadA-Dual deaminase comprises the mutations R26G, V28A, N46I, A48R, Y73S, and H96N (TadA-CD-14, SEQ ID NO: 3615) relative to the amino acid sequence of SEQ ID NO: 3594. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations R26G, V28A, A48R, Q71S, Y73S, and H96N (TadA-CD-15, SEQ ID NO: 3616) relative to the amino acid sequence of SEQ ID NO: 3594. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations R26G, V28A, N46L, A48R, and Y73P (TadA-CD-16, SEQ ID NO: 3617) relative to the amino acid sequence of SEQ ID NO: 3594. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations R26G, V28A, N46L, A48R, Y73P, and H96N (TadA-CD-17, SEQ ID NO: 3618) relative to the amino acid sequence of SEQ ID NO: 3594. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations R26G, V28A, Y73P, and H96N (TadA-CD-18, SEQ ID NO: 3619) relative to the amino acid sequence of

SEQ ID NO: 3594. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations R26G, V28A, N46V, A48R, Y73S, and H96N (TadA-CD-19, SEQ ID NO: 3620) relative to the amino acid sequence of SEQ ID NO: 3594. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations R26G, V28A, N46V, A48R, Y73P, and H96N (TadA-CD-20, SEQ ID NO: 3621) relative to the amino acid sequence of SEQ ID NO: 3594. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations R26G and N46L (TadA-CD-21, SEQ ID NO: 3622) relative to the amino acid sequence of SEQ ID NO: 3594. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations R26G, V28A, N46I, A48R, Y73P, and H96N (TadA-CD-22, SEQ ID NO: 3623) relative to the amino acid sequence of SEQ ID NO: 3594. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations R26G, V28A, N46V, A48R, Y73P, and H96N (TadA-CD-23, SEQ ID NO: 3624) relative to the amino acid sequence of SEQ ID NO: 3594. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations R26G, V28A, A48P, Y73H, T79P, and H96N (TadA-CD-24, SEQ ID NO: 3625) relative to the amino acid sequence of SEQ ID NO: 3594. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations R26G, N46I, and H96N (TadA-CD-25, SEQ ID NO: 3626) relative to the amino acid sequence of SEQ ID NO: 3594.

In some embodiments, the evolved TadA-Dual deaminase comprises the mutations R26G, V28A, N46V, A48R, Y73P, and H96N (TadA-CD-26, SEQ ID NO: 3627) relative to the amino acid sequence of SEQ ID NO: 3594. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations R26G, V28A, N46L, A48R, Y73S, and H96N (TadA-CD-27, SEQ ID NO: 3628) relative to the amino acid sequence of SEQ ID NO: 3594. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations R26G, V28A, N46C, A48R, H96N, and A162V (TadA-CD-28, SEQ ID NO: 3629) relative to the amino acid sequence of SEQ ID NO: 3594. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations R26G, V28A, N46V, A48R, Q71H, Y73P, and H96N (TadA-CD-29, SEQ ID NO: 3630) relative to the amino acid sequence of SEQ ID NO: 3594. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations R26G, V28A, N46C, A48R, Y73P, and H96N (TadA-CD-30, SEQ ID NO: 3631) relative to the amino acid sequence of SEQ ID NO: 3594. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations R26G, V28A, N46C, A48R, Y73P, H96N, and A162V (TadA-CD-31, SEQ ID NO: 3632) relative to the amino acid sequence of SEQ ID NO: 3594.

In some embodiments, the evolved TadA-Dual deaminase comprises the mutations R26G, V28A, N46V, A48R, Y73P, and H96N (TadA-CD-32, SEQ ID NO: 3633) relative to

the amino acid sequence of SEQ ID NO: 3594. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations R26G, V28A, N46V, A48R, Y73S, and H96N (TadA-CD-33, SEQ ID NO: 3634) relative to the amino acid sequence of SEQ ID NO: 3594. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations R26G, V28A, N46V, A48P, Y73S, and H96N (TadA-CD-34, SEQ ID NO: 3635) relative to the amino acid sequence of SEQ ID NO: 3594. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations R26G, V28A, N46C, A48R, Y73P, and H96N (TadA-CD-35, SEQ ID NO: 3636) relative to the amino acid sequence of SEQ ID NO: 3594. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations R26G, V28A, L34M, N46L, A48R, Y73P, and H96N (TadA-CD-36, SEQ ID NO: 3637) relative to the amino acid sequence of SEQ ID NO: 3594. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations R26G, V28A, N46L, A48R, Y73P, and H96N (TadA-CD-37, SEQ ID NO: 3638) relative to the amino acid sequence of SEQ ID NO: 3594. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations R26G, V28A, N46L, A48P, R64K, Y73P, and H96N (TadA-CD-38, SEQ ID NO: 3639) relative to the amino acid sequence of SEQ ID NO: 3594.

In some embodiments, the evolved TadA-Dual deaminase comprises the mutations N46L, S73P, and H154Q (TadA-CD-1, SEQ ID NO: 3602) relative to the amino acid sequence of SEQ ID NO: 3600. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations N46T (TadA-CD-2, SEQ ID NO: 3603) relative to the amino acid sequence of SEQ ID NO: 3600. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations N46T and H154Q (TadA-CD-3, SEQ ID NO: 3604) relative to the amino acid sequence of SEQ ID NO: 3600. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations N46V and H154Q (TadA-CD-4, SEQ ID NO: 3605) relative to the amino acid sequence of SEQ ID NO: 3600. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations N46V, S73P, G105S, and H154Q (TadA-CD-5, SEQ ID NO: 3606) relative to the amino acid sequence of SEQ ID NO: 3600. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations N46L, S73P, and H154Q (TadA-CD-6, SEQ ID NO: 3607) relative to the amino acid sequence of SEQ ID NO: 3600. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations G26R, N46L, R48P, S73P, N96H, and H154Q (TadA-CD-7, SEQ ID NO: 3608) relative to the amino acid sequence of SEQ ID NO: 3600. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations N46C, N96H, and H154Q (TadA-CD-8, SEQ ID NO: 3609) relative to the amino acid sequence of SEQ ID NO: 3600. In some embodiments,

the evolved TadA-Dual deaminase comprises the mutations N46V, S73P, and H154Q (TadA-CD-9, SEQ ID NO: 3610) relative to the amino acid sequence of SEQ ID NO: 3600. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations N46V, Q71H, S73P, and H154Q (TadA-CD-10, SEQ ID NO: 3611) relative to the amino acid sequence of SEQ ID NO: 3600. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations N46L and H154Q (TadA-CD-11, SEQ ID NO: 3612) relative to the amino acid sequence of SEQ ID NO: 3600. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations N46C, S73P, and H154Q (TadA-CD-12, SEQ ID NO: 3613) relative to the amino acid sequence of SEQ ID NO: 3600. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations N46C, S73P, H154Q, and A162V (TadA-CD-13, SEQ ID NO: 3614) relative to the amino acid sequence of SEQ ID NO: 3600.

In some embodiments, the evolved TadA-Dual deaminase comprises the mutations N46I and H154Q (TadA-CD-14, SEQ ID NO: 3615) relative to the amino acid sequence of SEQ ID NO: 3600. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations Q71S and H154Q (TadA-CD-15, SEQ ID NO: 3616) relative to the amino acid sequence of SEQ ID NO: 3594. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations N46L, S73P, N79T, and N96H (TadA-CD-16, SEQ ID NO: 3617) relative to the amino acid sequence of SEQ ID NO: 3600. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations N46L, S73P, N79T (TadA-CD-17, SEQ ID NO: 3618) relative to the amino acid sequence of SEQ ID NO: 3600. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations R48A, S73P, and N79T (TadA-CD-18, SEQ ID NO: 3619) relative to the amino acid sequence of SEQ ID NO: 3600. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations N46V and N79T (TadA-CD-19, SEQ ID NO: 3620) relative to the amino acid sequence of SEQ ID NO: 3600. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations N46V, S73P, and N79T (TadA-CD-20, SEQ ID NO: 3621) relative to the amino acid sequence of SEQ ID NO: 3600. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations A28V, N46L, R48A, S73Y, N79T, and N96H (TadA-CD-21, SEQ ID NO: 3622) relative to the amino acid sequence of SEQ ID NO: 3600. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations N46I, S73P, and N79T (TadA-CD-22, SEQ ID NO: 3623) relative to the amino acid sequence of SEQ ID NO: 3600. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations N46V, S73P, N79T, and G106S (TadA-CD-23, SEQ ID NO: 3624) relative to the amino acid sequence of SEQ ID NO: 3600. In some embodiments, the evolved TadA-Dual deaminase

comprises the mutations R48P, S73H, and N79P (TadA-CD-24, SEQ ID NO: 3625) relative to the amino acid sequence of SEQ ID NO: 3600. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations A28V, N46I, R48A, S73Y, and N79T (TadA-CD-25, SEQ ID NO: 3626) relative to the amino acid sequence of SEQ ID NO: 3600.

- 5 In some embodiments, the evolved TadA-Dual deaminase comprises the mutations N46V and S73P (TadA-CD-26, SEQ ID NO: 3627) relative to the amino acid sequence of SEQ ID NO: 3600. In some embodiments, the evolved TadA-Dual deaminase comprises the mutation N46L (TadA-CD-27, SEQ ID NO: 3628) relative to the amino acid sequence of SEQ ID NO: 3600. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations N46C, S73Y, and A162V (TadA-CD-28, SEQ ID NO: 3629) relative to the amino acid sequence of SEQ ID NO: 3600. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations N46V, Q71H, and S73P (TadA-CD-29, SEQ ID NO: 3630) relative to the amino acid sequence of SEQ ID NO: 3600. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations N46C and S73P (TadA-CD-30, SEQ ID NO: 3631) relative to the amino acid sequence of SEQ ID NO: 3600. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations N46C, S73P, and A162V (TadA-CD-31, SEQ ID NO: 3632) relative to the amino acid sequence of SEQ ID NO: 3600. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations N46V and S73P (TadA-CD-32, SEQ ID NO: 3633) relative to the amino acid sequence of SEQ ID NO: 3600. In some embodiments, the evolved TadA-Dual deaminase comprises the mutation N46V (TadA-CD-33, SEQ ID NO: 3634) relative to the amino acid sequence of SEQ ID NO: 3600. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations N46V and R48P (TadA-CD-34, SEQ ID NO: 3635) relative to the amino acid sequence of SEQ ID NO: 3600. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations N46CV and S73P (TadA-CD-35, SEQ ID NO: 3636) relative to the amino acid sequence of SEQ ID NO: 3600. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations L34M, N46L and S73P (TadA-CD-36, SEQ ID NO: 3637) relative to the amino acid sequence of SEQ ID NO: 3600. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations N46L and S73P (TadA-CD-37, SEQ ID NO: 3638) relative to the amino acid sequence of SEQ ID NO: 3600. In some embodiments, the evolved TadA-Dual deaminase comprises the mutations N46L, R48P, R64K and S73P (TadA-CD-38, SEQ ID NO: 3639) relative to the amino acid sequence of SEQ ID NO: 3600.

In some embodiments, the TadA-CDs evolved from TadA-dual comprise at least 80%, 85%, 90%, 95%, 98%, 99%, or 99.5% identical to any of the amino acid sequences of SEQ ID NOs: 39, 41-54, and 359-383.

Exemplary TadA-derived cytosine base editor amino acid sequences include: TadA-
 5 CDa base editor (SpCas9n napDNAbp domain) (TadCBEa) (SEQ ID NO: 3640), TadA-CDb
 base editor (SpCas9n napDNAbp domain) (TadCBEb) (SEQ ID NO: 3641), TadA-CDc base
 editor (SpCas9n napDNAbp domain) (TadCBEc) (SEQ ID NO: 3642), TadA-CDd base
 editor (SpCas9n napDNAbp domain) (TadCBEd) (SEQ ID NO: 3643), TadA-CDe base
 editor (SpCas9n napDNAbp domain) (TadCBEE) (SEQ ID NO: 3644), TadA-CDa(V106W)
 10 base editor (SpCas9n napDNAbp domain) (TadCBEa(V106W)) (SEQ ID NO: 3645), TadA-
 CDd(V106W) base editor (SpCas9n napDNAbp domain) (TadCBEd(V106W)) (SEQ ID NO:
 3646), TadA-CDf base editor (SpCas9n napDNAbp domain) (TadCBEf) (SEQ ID NO:
 3647), TadA-CDg base editor (SpCas9n napDNAbp domain) (TadCBEG) (SEQ ID NO:
 3648), TadA-CDa:eNme2Cas9 base editor (SEQ ID NO: 3649), TadA-CDa:SaCas9 base
 15 editor (SEQ ID NO: 3650), TadA-CDa:SpCas9-NG base editor (SEQ ID NO: 3651), TadA-
 CDa:enCjCas9 base editor (SEQ ID NO: 3652).

Exemplary polynucleotides encoding TadA-derived cytosine base editors of the
 disclosure include: TadCBEa-eNme2-C-BE4max vector (SEQ ID NO: 3653), TadCBEa-
 enCjCas9-BE4max vector (SEQ ID NO: 3654), TadCBEa-SpCas9-BE4max vector (SEQ ID
 20 NO: 3655), TadCBEa-SaCas9-BE4max vector (SEQ ID NO: 3656), TadCBEa-SpCas9-NG-
 BE4max vector (SEQ ID NO: 3657).

Guide Polynucleotides

A polynucleotide programmable nucleotide binding domain, when in conjunction
 25 with a bound guide polynucleotide (*e.g.*, gRNA), can specifically bind to a target
 polynucleotide sequence (*i.e.*, via complementary base pairing between bases of the bound
 guide nucleic acid and bases of the target polynucleotide sequence) and thereby localize the
 base editor to the target nucleic acid sequence desired to be edited. In some embodiments, the
 target polynucleotide sequence comprises single-stranded DNA or double-stranded DNA. In
 30 some embodiments, the target polynucleotide sequence comprises RNA. In some
 embodiments, the target polynucleotide sequence comprises a DNA-RNA hybrid.

In an embodiment, a guide polynucleotide described herein can be RNA or DNA. In
 one embodiment, the guide polynucleotide is a gRNA.

In some embodiments, the guide polynucleotide is at least one single guide RNA (“sgRNA” or “gRNA”). In some embodiments, a guide polynucleotide comprises two or more individual polynucleotides, which can interact with one another via for example complementary base pairing (*e.g.*, a dual guide polynucleotide, dual gRNA). For example, a guide polynucleotide can comprise a CRISPR RNA (crRNA) and a trans-activating CRISPR RNA (tracrRNA) or can comprise one or more trans-activating CRISPR RNA (tracrRNA).

A guide polynucleotide may include natural or non-natural (or unnatural) nucleotides (*e.g.*, peptide nucleic acid or nucleotide analogs). In some cases, the targeting region of a guide nucleic acid sequence (*e.g.*, a spacer) can be at least 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length.

In some embodiments, the methods described herein can utilize an engineered Cas protein. A guide RNA (gRNA) is a short synthetic RNA composed of a scaffold sequence necessary for Cas-binding and a user-defined ~20 nucleotide spacer that defines the genomic target to be modified. Exemplary gRNA scaffold sequences are provided in the sequence listing as SEQ ID NOs: 317-327 and 425. Thus, a skilled artisan can change the genomic target of the Cas protein specificity is partially determined by how specific the gRNA targeting sequence is for the genomic target compared to the rest of the genome. In embodiments, the spacer is about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 22, 23, 24, 25, or more nucleotides in length. The spacer of a gRNA can be or can be about 19, 20, or 21 nucleotides in length.

A gRNA or a guide polynucleotide can target any exon or intron of a gene target. In some embodiments, a composition comprises multiple gRNAs that all target the same exon or multiple gRNAs that target different exons. An exon and/or an intron of a gene can be targeted. A gRNA or a guide polynucleotide can target a nucleic acid sequence of about 20 nucleotides or less than about 20 nucleotides (*e.g.*, at least about 5, 10, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30 nucleotides), or anywhere between about 1-100 nucleotides (*e.g.*, 5, 10, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40, 50, 60, 70, 80, 90, 100). A target nucleic acid sequence can be or can be about 20 bases immediately 5' of the first nucleotide of the PAM. A gRNA can target a nucleic acid sequence. A target nucleic acid can be at least or at least about 1-10, 1-20, 1-30, 1-40, 1-50, 1-60, 1-70, 1-80, 1-90, or 1-100 nucleotides.

The guide polynucleotides can comprise standard ribonucleotides, modified ribonucleotides (*e.g.*, pseudouridine), ribonucleotide isomers, and/or ribonucleotide analogs.

In some embodiments, a base editor system may comprise multiple guide polynucleotides, *e.g.*, gRNAs. For example, the gRNAs may target to one or more target loci (*e.g.*, at least 1 gRNA, at least 2 gRNA, at least 5 gRNA, at least 10 gRNA, at least 20 gRNA,

at least 30 g RNA, at least 50 gRNA) comprised in a base editor system. The multiple gRNA sequences can be tandemly arranged and may be separated by a direct repeat.

Modified Polynucleotides

5 To enhance expression, stability, and/or genomic/base editing efficiency, and/or reduce possible toxicity, the base editor-coding sequence (e.g., mRNA) and/or the guide polynucleotide (e.g., gRNA) can be modified to include one or more modified nucleotides and/or chemical modifications, e.g. using pseudo-uridine, 5-Methyl-cytosine, 2'-O-methyl-3'-phosphonoacetate, 2'-O-methyl thioPACE (MSP), 2'-O-methyl-PACE (MP), 2'-fluoro RNA
10 (2'-F-RNA), =constrained ethyl (S-cEt), 2'-O-methyl ('M'), 2'-O-methyl-3'-phosphorothioate ('MS'), 2'-O-methyl-3'-thiophosphonoacetate ('MSP'), 5-methoxyuridine, phosphorothioate, and N1-Methylpseudouridine. Chemically protected gRNAs can enhance stability and editing efficiency *in vivo* and *ex vivo*. Methods for using chemically modified mRNAs and guide RNAs are known in the art and described, for example, by Jiang et al., Chemical
15 modifications of adenine base editor mRNA and guide RNA expand its application scope. Nat Commun 11, 1979 (2020). doi.org/10.1038/s41467-020-15892-8, Callum et al., N1-Methylpseudouridine substitution enhances the performance of synthetic mRNA switches in cells, *Nucleic Acids Research*, Volume 48, Issue 6, 06 April 2020, Page e35, and Andries et al., *Journal of Controlled Release*, Volume 217, 10 November 2015, Pages 337-344, each of
20 which is incorporated herein by reference in its entirety.

In some embodiments, the guide polynucleotide comprises one or more modified nucleotides at the 5' end and/or the 3' end of the guide. In some embodiments, the guide polynucleotide comprises two, three, four or more modified nucleosides at the 5' end and/or the 3' end of the guide. In some embodiments, the guide polynucleotide comprises two, three,
25 four or more modified nucleosides at the 5' end and/or the 3' end of the guide.

In some embodiments, the guide comprises at least about 50%-75% modified nucleotides. In some embodiments, the guide comprises at least about 85% or more modified nucleotides. In some embodiments, at least about 1-5 nucleotides at the 5' end of the gRNA are modified and at least about 1-5 nucleotides at the 3' end of the gRNA are modified. In
30 some embodiments, at least about 3-5 contiguous nucleotides at each of the 5' and 3' termini of the gRNA are modified. In some embodiments, at least about 20% of the nucleotides present in a direct repeat or anti-direct repeat are modified. In some embodiments, at least about 50% of the nucleotides present in a direct repeat or anti-direct repeat are modified. In some embodiments, at least about 50-75% of the nucleotides present in a direct repeat or anti-

direct repeat are modified. In some embodiments, at least about 100 of the nucleotides present in a direct repeat or anti-direct repeat are modified. In some embodiments, at least about 20% or more of the nucleotides present in a hairpin present in the gRNA scaffold are modified. In some embodiments, at least about 50% or more of the nucleotides present in a hairpin present in the gRNA scaffold are modified. In some embodiments, the guide comprises a variable length spacer. In some embodiments, the guide comprises a 20-40 nucleotide spacer. In some embodiments, the guide comprises a spacer comprising at least about 20-25 nucleotides or at least about 30-35 nucleotides. In some embodiments, the spacer comprises modified nucleotides. In some embodiments, the guide comprises two or more of the following:

- at least about 1-5 nucleotides at the 5' end of the gRNA are modified and at least about 1-5 nucleotides at the 3' end of the gRNA are modified;
- at least about 20% of the nucleotides present in a direct repeat or anti-direct repeat are modified;
- at least about 50-75% of the nucleotides present in a direct repeat or anti-direct repeat are modified;
- at least about 20% or more of the nucleotides present in a hairpin present in the gRNA scaffold are modified;
- a variable length spacer; and
- a spacer comprising modified nucleotides.

In embodiments, the gRNA contains numerous modified nucleotides and/or chemical modifications. Such modifications can increase base editing ~2 fold *in vivo* or *in vitro*. In embodiments, the gRNA comprises 2'-O-methyl or phosphorothioate modifications. In an embodiment, the gRNA comprises 2'-O-methyl and phosphorothioate modifications. In an embodiment, the modifications increase base editing by at least about 2 fold.

A guide polynucleotide can comprise one or more modifications to provide a nucleic acid with a new or enhanced feature. A guide polynucleotide can comprise a nucleic acid affinity tag. A guide polynucleotide can comprise synthetic nucleotide, synthetic nucleotide analog, nucleotide derivatives, and/or modified nucleotides.

A gRNA or a guide polynucleotide can also be modified by 5' adenylate, 5' guanosine-triphosphate cap, 5' N7-Methylguanosine-triphosphate cap, 5' triphosphate cap, 3' phosphate, 3' thiophosphate, 5' phosphate, 5' thiophosphate, Cis-Syn thymidine dimer, trimers, C12 spacer, C3 spacer, C6 spacer, dSpacer, PC spacer, rSpacer, Spacer 18, Spacer 9,

3'-3' modifications, 2'-*O*-methyl thioPACE (MSP), 2'-*O*-methyl-PACE (MP), and constrained ethyl (S-cEt), 5'-5' modifications, abasic, acridine, azobenzene, biotin, biotin BB, biotin TEG, cholesteryl TEG, desthiobiotin TEG, DNP TEG, DNP-X, DOTA, dT-Biotin, dual biotin, PC biotin, psoralen C2, psoralen C6, TINA, 3' DABCYL, black hole quencher 1, 5 black hole quencher 2, DABCYL SE, dT-DABCYL, IRDye QC-1, QSY-21, QSY-35, QSY-7, QSY-9, carboxyl linker, thiol linkers, 2'-deoxyribonucleoside analog purine, 2'-deoxyribonucleoside analog pyrimidine, ribonucleoside analog, 2'-*O*-methyl ribonucleoside analog, sugar modified analogs, wobble/universal bases, fluorescent dye label, 2'-fluoro RNA, 2'-*O*-methyl RNA, methylphosphonate, phosphodiester DNA, phosphodiester RNA, 10 phosphothioate DNA, phosphorothioate RNA, UNA, pseudouridine-5'-triphosphate, 5'-methylcytidine-5'-triphosphate, or any combination thereof.

In some cases, a phosphorothioate enhanced RNA gRNA can inhibit RNase A, RNase T1, calf serum nucleases, or any combinations thereof. These properties can allow the use of PS-RNA gRNAs to be used in applications where exposure to nucleases is of high probability 15 *in vivo* or *in vitro*. For example, phosphorothioate (PS) bonds can be introduced between the last 3-5 nucleotides at the 5'- or 3'-end of a gRNA which can inhibit exonuclease degradation. In some cases, phosphorothioate bonds can be added throughout an entire gRNA to reduce attack by endonucleases.

20 ***Fusion Proteins or Complexes Comprising a Nuclear Localization Sequence (NLS)***

In some embodiments, the fusion proteins or complexes provided herein further comprise one or more (*e.g.*, 2, 3, 4, 5) nuclear targeting sequences, for example a nuclear localization sequence (NLS). In one embodiment, a bipartite NLS is used. In some 25 embodiments, a NLS comprises an amino acid sequence that facilitates the importation of a protein, that comprises an NLS, into the cell nucleus (*e.g.*, by nuclear transport). In some embodiments, the NLS is fused to the N-terminus or the C-terminus of the fusion protein. In some embodiments, the NLS is fused to the C-terminus or N-terminus of an nCas9 domain or a dCas9 domain. In some embodiments, the NLS is fused to the N-terminus or C-terminus of the Cas12 domain. In some embodiments, the NLS is fused to the N-terminus or C-terminus 30 of the cytidine or adenosine deaminase. In some embodiments, the NLS is fused to the fusion protein via one or more linkers. In some embodiments, the NLS is fused to the fusion protein without a linker. In some embodiments, the NLS comprises an amino acid sequence of any one of the NLS sequences provided or referenced herein. Additional nuclear localization sequences are known in the art and would be apparent to the skilled artisan. For example,

NLS sequences are described in Plank *et al.*, PCT/EP2000/011690, the contents of which are incorporated herein by reference for their disclosure of exemplary nuclear localization sequences.

In some embodiments, the NLS is present in a linker or the NLS is flanked by linkers, for example described herein. A bipartite NLS comprises two basic amino acid clusters, which are separated by a relatively short spacer sequence (hence bipartite - 2 parts, while monopartite NLSs are not). The NLS of nucleoplasmin, KR [PAATKKAGQA] KKKK (SEQ ID NO: 191), is the prototype of the ubiquitous bipartite signal: two clusters of basic amino acids, separated by a spacer of about 10 amino acids. The sequence of an exemplary bipartite NLS follows:
PKKKRKVEGADKRTADGSEFESPKKKRKV (SEQ ID NO: 328).

In some embodiments, any of the fusion proteins or complexes provided herein comprise an NLS comprising the amino acid sequence EGADKRTADGSEFESPKKKRKV (amino acids 8 to 29 of SEQ ID NO 328). In some embodiments, any of the adenosine base editors provided herein comprise an NLS comprising the amino acid sequence EGADKRTADGSEFESPKKKRKV (amino acids 8 to 29 of SEQ ID NO: 328). In some embodiments, the NLS is at a C-terminal portion of the adenosine base editor. In some embodiments, the NLS is at the C-terminus of the adenosine base editor.

20 ***Additional Domains***

A base editor described herein can include any domain which helps to facilitate the nucleobase editing, modification or altering of a nucleobase of a polynucleotide. In some embodiments, a base editor comprises a polynucleotide programmable nucleotide binding domain (*e.g.*, Cas9), a nucleobase editing domain (*e.g.*, deaminase domain), and one or more additional domains. In some embodiments, the additional domain can facilitate enzymatic or catalytic functions of the base editor, binding functions of the base editor, or be inhibitors of cellular machinery (*e.g.*, enzymes) that could interfere with the desired base editing result. In some embodiments, a base editor comprises a nuclease, a nickase, a recombinase, a deaminase, a methyltransferase, a methylase, an acetylase, an acetyltransferase, a transcriptional activator, or a transcriptional repressor domain.

In some embodiments, a base editor comprises an uracil glycosylase inhibitor (UGI) domain. In some cases, a base editor is expressed in a cell in trans with a UGI polypeptide. In some embodiments, cellular DNA repair response to the presence of U: G heteroduplex DNA

can be responsible for a reduction in nucleobase editing efficiency in cells. In such embodiments, uracil DNA glycosylase (UDG) can catalyze removal of U from DNA in cells, which can initiate base excision repair (BER), mostly resulting in reversion of the U:G pair to a C:G pair. In such embodiments, BER can be inhibited in base editors comprising one or more domains that bind the single strand, block the edited base, inhibit UGI, inhibit BER, protect the edited base, and /or promote repairing of the non-edited strand. Thus, this disclosure contemplates a base editor fusion protein or complex comprising a UGI domain and/or a uracil stabilizing protein (USP) domain.

10 **BASE EDITOR SYSTEM**

Provided herein are systems, compositions, and methods for editing a nucleobase using a base editor system. In some embodiments, the base editor system comprises (1) a base editor (BE) comprising a polynucleotide programmable nucleotide binding domain and a nucleobase editing domain (*e.g.*, a deaminase domain) for editing the nucleobase; and (2) a guide polynucleotide (*e.g.*, guide RNA) in conjunction with the polynucleotide programmable nucleotide binding domain. In some embodiments, the base editor system is a cytidine base editor (CBE) or an adenosine base editor (ABE). In some embodiments, the polynucleotide programmable nucleotide binding domain is a polynucleotide programmable DNA or RNA binding domain. In some embodiments, the nucleobase editing domain is a deaminase domain. In some embodiments, a deaminase domain can be a cytidine deaminase or an cytosine deaminase. In some embodiments, a deaminase domain can be an adenine deaminase or an adenosine deaminase. In some embodiments, the adenosine base editor can deaminate adenine in DNA. In some embodiments, the base editor is capable of deaminating a cytidine in DNA.

25 Use of the base editor system provided herein comprises the steps of: (a) contacting a target nucleotide sequence of a polynucleotide (*e.g.*, double- or single stranded DNA or RNA) of a subject with a base editor system comprising a nucleobase editor (*e.g.*, an adenosine base editor or a cytidine base editor) and a guide polynucleotide (*e.g.*, gRNA), wherein the target nucleotide sequence comprises a targeted nucleobase pair; (b) inducing strand separation of said target region; (c) converting a first nucleobase of said target nucleobase pair in a single strand of the target region to a second nucleobase; and (d) cutting no more than one strand of said target region, where a third nucleobase complementary to the first nucleobase base is replaced by a fourth nucleobase complementary to the second nucleobase. It should be appreciated that in some embodiments, step (b) is omitted. In some

embodiments, said targeted nucleobase pair is a plurality of nucleobase pairs in one or more genes. In some embodiments, the base editor system provided herein is capable of multiplex editing of a plurality of nucleobase pairs in one or more genes. In some embodiments, the plurality of nucleobase pairs is located in the same gene. In some embodiments, the plurality of nucleobase pairs is located in one or more genes, wherein at least one gene is located in a different locus.

The components of a base editor system (e.g., a deaminase domain, a guide RNA, and/or a polynucleotide programmable nucleotide binding domain) may be associated with each other covalently or non-covalently. For example, in some embodiments, the deaminase domain can be targeted to a target nucleotide sequence by a polynucleotide programmable nucleotide binding domain, optionally where the polynucleotide programmable nucleotide binding domain is complexed with a polynucleotide (e.g., a guide RNA). In some embodiments, a polynucleotide programmable nucleotide binding domain can be fused or linked to a deaminase domain. In some embodiments, a polynucleotide programmable nucleotide binding domain can target a deaminase domain to a target nucleotide sequence by non-covalently interacting with or associating with the deaminase domain. For example, in some embodiments, the nucleobase editing component (e.g., the deaminase component) comprises an additional heterologous portion or domain that is capable of interacting with, associating with, or capable of forming a complex with a corresponding heterologous portion, antigen, or domain that is part of a polynucleotide programmable nucleotide binding domain and/or a guide polynucleotide (e.g., a guide RNA) complexed therewith. In some embodiments, the polynucleotide programmable nucleotide binding domain, and/or a guide polynucleotide (e.g., a guide RNA) complexed therewith, comprises an additional heterologous portion or domain that is capable of interacting with, associating with, or capable of forming a complex with a corresponding heterologous portion, antigen, or domain that is part of a nucleobase editing domain (e.g., the deaminase component). In some embodiments, the additional heterologous portion may be capable of binding to, interacting with, associating with, or forming a complex with a polypeptide. In some embodiments, the additional heterologous portion may be capable of binding to, interacting with, associating with, or forming a complex with a polynucleotide. In some embodiments, the additional heterologous portion may be capable of binding to a guide polynucleotide. In some embodiments, the additional heterologous portion may be capable of binding to a polypeptide linker. In some embodiments, the additional heterologous portion is capable of binding to a polynucleotide linker. An additional heterologous portion may be a protein domain. In some

embodiments, an additional heterologous portion comprises a polypeptide, such as a 22 amino acid RNA-binding domain of the lambda bacteriophage antiterminator protein N (N22p), a 2G12 IgG homodimer domain, an ABI, an antibody (*e.g.* an antibody that binds a component of the base editor system or a heterologous portion thereof) or fragment thereof

5 (*e.g.* heavy chain domain 2 (CH2) of IgM (MHD2) or IgE (EHD2), an immunoglobulin Fc region, a heavy chain domain 3 (CH3) of IgG or IgA, a heavy chain domain 4 (CH4) of IgM or IgE, an Fab, an Fab2, miniantibodies, and/or ZIP antibodies), a barnase-barstar dimer domain, a Bcl-xL domain, a Calcineurin A (CAN) domain, a Cardiac phospholamban transmembrane pentamer domain, a collagen domain, a Com RNA binding protein domain

10 (*e.g.* SfMu Com coat protein domain, and SfMu Com binding protein domain), a Cyclophilin-Fas fusion protein (CyP-Fas) domain, a Fab domain, an Fe domain, a fibrin foldon domain, an FK506 binding protein (FKBP) domain, an FKBP binding domain (FRB) domain of mTOR, a foldon domain, a fragment X domain, a GAI domain, a GID1 domain, a Glycophorin A transmembrane domain, a GyrB domain, a Halo tag, an HIV Gp41

15 trimerisation domain, an HPV45 oncoprotein E7 C-terminal dimer domain, a hydrophobic polypeptide, a K Homology (KH) domain, a Ku protein domain (*e.g.*, a Ku heterodimer), a leucine zipper, a LOV domain, a mitochondrial antiviral-signaling protein CARD filament domain, an MS2 coat protein domain (MCP), a non-natural RNA aptamer ligand that binds a corresponding RNA motif/aptamer, a parathyroid hormone dimerization domain, a PP7 coat

20 protein (PCP) domain, a PSD95-Dlg1-zo-1 (PDZ) domain, a PYL domain, a SNAP tag, a SpyCatcher moiety, a SpyTag moiety, a streptavidin domain, a streptavidin-binding protein domain, a streptavidin binding protein (SBP) domain, a telomerase Sm7 protein domain (*e.g.* Sm7 homoheptamer or a monomeric Sm-like protein), and/or fragments thereof. In

embodiments, an additional heterologous portion comprises a polynucleotide (*e.g.*, an RNA motif), such as an MS2 phage operator stem-loop (*e.g.*, an MS2, an MS2 C-5 mutant, or an MS2 F-5 mutant), a non-natural RNA motif, a PP7 operator stem-loop, an SfMu phate Com stem-loop, a steril alpha motif, a telomerase Ku binding motif, a telomerase Sm7 binding motif,, and/or fragments thereof . Non-limiting examples of additional heterologous portions

25 include polypeptides with at least about 85% sequence identity to any one or more of SEQ ID

30 NOs: 380, 382, 384, 386-388, or fragments thereof. Non-limiting examples of additional heterologous portions include polynucleotides with at least about 85% sequence identity to any one or more of SEQ ID NOs: 379, 381, 383, 385, or fragments thereof.

In some instances, components of the base editing system are associated with one another through the interaction of leucine zipper domains (*e.g.*, SEQ ID NOs: 387 and 388).

In some cases, components of the base editing system are associated with one another through polypeptide domains (e.g., FokI domains) that associate to form protein complexes containing about, at least about, or no more than about 1, 2 (i.e., dimerize), 3, 4, 5, 6, 7, 8, 9, 10 polypeptide domain units, optionally the polypeptide domains may include alterations that
5 reduce or eliminate an activity thereof.

In some instances, components of the base editing system are associated with one another through the interaction of multimeric antibodies or fragments thereof (e.g., IgG, IgD, IgA, IgM, IgE, a heavy chain domain 2 (CH2) of IgM (MHD2) or IgE (EHD2), an immunoglobulin Fc region, a heavy chain domain 3 (CH3) of IgG or IgA, a heavy chain
10 domain 4 (CH4) of IgM or IgE, an Fab, and an Fab2). In some instances, the antibodies are dimeric, trimeric, or tetrameric. In embodiments, the dimeric antibodies bind a polypeptide or polynucleotide component of the base editing system.

In some cases, components of the base editing system are associated with one another through the interaction of a polynucleotide-binding protein domain(s) with a
15 polynucleotide(s). In some instances, components of the base editing system are associated with one another through the interaction of one or more polynucleotide-binding protein domains with polynucleotides that are self-complementary and/or complementary to one another so that complementary binding of the polynucleotides to one another brings into association their respective bound polynucleotide-binding protein domain(s).

In some instances, components of the base editing system are associated with one another through the interaction of a polypeptide domain(s) with a small molecule(s) (e.g., chemical inducers of dimerization (CIDs), also known as “dimerizers”). Non-limiting examples of CIDs include those disclosed in Amara, *et al.*, “A versatile synthetic dimerizer for the regulation of protein-protein interactions,” *PNAS*, 94:10618-10623 (1997); and Voß,
25 *et al.* “Chemically induced dimerization: reversible and spatiotemporal control of protein function in cells,” *Current Opinion in Chemical Biology*, 28:194-201 (2015), the disclosures of each of which are incorporated herein by reference in their entireties for all purposes. In some embodiments, the base editor inhibits base excision repair (BER) of the edited strand. In some embodiments, the base editor protects or binds the non-edited strand. In some
30 embodiments, the base editor comprises UGI activity or USP activity. In some embodiments, the base editor comprises a catalytically inactive inosine-specific nuclease.

The base editors of the present disclosure can comprise any domain, feature or amino acid sequence which facilitates the editing of a target polynucleotide sequence. For example, in some embodiments, the base editor comprises a nuclear localization sequence (NLS). In

some embodiments, an NLS of the base editor is localized between a deaminase domain and a polynucleotide programmable nucleotide binding domain. In some embodiments, an NLS of the base editor is localized C-terminal to a polynucleotide programmable nucleotide binding domain.

- 5 Protein domains included in the fusion protein can be a heterologous functional domain. Non-limiting examples of protein domains which can be included in the fusion protein include a deaminase domain (e.g., cytidine deaminase and/or adenosine deaminase), a uracil glycosylase inhibitor (UGI) domain, epitope tags, and reporter gene sequences. In some embodiments, the adenosine base editor (ABE) can deaminate adenine in DNA. In
- 10 some embodiments, ABE is generated by replacing APOBEC1 component of BE3 with natural or engineered *E. coli* TadA, human ADAR2, mouse ADA, or human ADAT2. In some embodiments, ABE comprises an evolved TadA variant. In some embodiments, the base editor is ABE8.1, which comprises or consists essentially of the following sequence or a fragment thereof having adenosine deaminase activity: SEQ ID NO: 331. Other ABE8
- 15 sequences are provided in the attached sequence listing (SEQ ID NOs: 332-354).

- In some embodiments, the base editor includes an adenosine deaminase variant comprising an amino acid sequence, which contains alterations relative to an ABE 7*10 reference sequence, as described herein. The term “monomer” as used in **Table 7** refers to a monomeric form of TadA*7.10 comprising the alterations described. The term “heterodimer”
- 20 as used in **Table 7** refers to the specified wild-type *E. coli* TadA adenosine deaminase fused to a TadA*7.10 comprising the alterations as described.

Table 7. Adenosine Deaminase Base Editor Variants

ABE	Adenosine Deaminase	Adenosine Deaminase Description
ABE-605m	MSP605	monomer_TadA*7.10 + V82G + Y147T + Q154S
ABE-680m	MSP680	monomer_TadA*7.10 + I76Y + V82G + Y147T + Q154S
ABE-823m	MSP823	monomer_TadA*7.10 + L36H + V82G + Y147T + Q154S + N157K
ABE-824m	MSP824	monomer_TadA*7.10 + V82G + Y147D + F149Y + Q154S + D167N
ABE-825m	MSP825	monomer_TadA*7.10 + L36H + V82G + Y147D + F149Y + Q154S + N157K + D167N
ABE-827m	MSP827	monomer_TadA*7.10 + L36H + I76Y + V82G + Y147T + Q154S + N157K
ABE-828m	MSP828	monomer_TadA*7.10 + I76Y + V82G + Y147D + F149Y + Q154S + D167N

ABE	Adenosine Deaminase	Adenosine Deaminase Description
ABE-829m	MSP829	monomer_TadA*7.10 + L36H + I76Y + V82G + Y147D + F149Y + Q154S + N157K + D167N
ABE-605d	MSP605	heterodimer_(WT)+(TadA*7.10 + V82G + Y147T + Q154S)
ABE-680d	MSP680	heterodimer_(WT)+(TadA*7.10 + I76Y + V82G + Y147T + Q154S)
ABE-823d	MSP823	heterodimer_(WT)+(TadA*7.10 + L36H + V82G + Y147T + Q154S + N157K)
ABE-824d	MSP824	heterodimer_(WT)+(TadA*7.10 + V82G + Y147D + F149Y + Q154S + D167N)
ABE-825d	MSP825	heterodimer_(WT)+(TadA*7.10 + L36H + V82G + Y147D + F149Y + Q154S + N157K + D167N)
ABE-827d	MSP827	heterodimer_(WT)+(TadA*7.10 + L36H + I76Y + V82G + Y147T + Q154S + N157K)
ABE-828d	MSP828	heterodimer_(WT)+(TadA*7.10 + I76Y + V82G + Y147D + F149Y + Q154S + D167N)
ABE-829d	MSP829	heterodimer_(WT)+(TadA*7.10 + L36H + I76Y + V82G + Y147D + F149Y + Q154S + N157K + D167N)

In some embodiments, the base editor comprises a domain comprising all or a portion (e.g., a functional portion) of a uracil glycosylase inhibitor (UGI) or a uracil stabilizing protein (USP) domain.

5

Linkers

In certain embodiments, linkers may be used to link any of the peptides or peptide domains of the disclosure. The linker may be as simple as a covalent bond, or it may be a polymeric linker many atoms in length. In certain embodiments, the linker is a polypeptide or based on amino acids. In other embodiments, the linker is not peptide-like. In certain
10
embodiments, the linker is a covalent bond (e.g., a carbon-carbon bond, disulfide bond, carbon-heteroatom bond, *etc.*).

In some embodiments, any of the fusion proteins provided herein, comprise a cytidine or adenosine deaminase and a Cas9 domain that are fused to each other via a linker. Various
15
linker lengths and flexibilities between the cytidine or adenosine deaminase and the Cas9 domain can be employed (e.g., ranging from very flexible linkers of the form (GGGS)_n (SEQ ID NO: 246), (GGGGS)_n (SEQ ID NO: 247), and (G)_n to more rigid linkers of the form (EAAAK)_n (SEQ ID NO: 248), (SGGS)_n (SEQ ID NO: 355), SGSETPGTSESATPES (SEQ ID NO: 249) (see, e.g., Guilinger JP, *et al.* Fusion of catalytically inactive Cas9 to FokI nuclease
20
improves the specificity of genome modification. Nat. Biotechnol. 2014; 32(6): 577-82; the entire contents are incorporated herein by reference) and (XP)_n in order to achieve the

optimal length for activity for the cytidine or adenosine deaminase nucleobase editor. In some embodiments, n is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15. In some embodiments, the linker comprises a (GGG)_n motif, wherein n is 1, 3, or 7. In some embodiments, cytidine deaminase or adenosine deaminase and the Cas9 domain of any of the fusion proteins

- 5 provided herein are fused via a linker comprising the amino acid sequence SGSETPGTSESATPES (SEQ ID NO: 249), which can also be referred to as the XTEN linker.

In some embodiments, the domains of the base editor are fused via a linker that comprises the amino acid sequence of:

- 10 SGGSSGSETPGTSESATPESGGGS (SEQ ID NO: 356),
 SGGSSGGSSGSETPGTSESATPESGGSSGGGS (SEQ ID NO: 357),
 GGGSGSPGSPAGSPTSTEEGTSESATPESGPGTSTEPSEGSAPGSPAGSPTSTEEGTSTEPS
 EGSAPGTSTEPSEGSAPGTSESATPESGPGSEPATSGGSSGGGS (SEQ ID NO: 358),
 EGGSEEEEEESGS (SEQ ID NO: 3573), or KGPKPKKEESEK (SEQ ID NO: 3574).

- 15 In some embodiments, domains of the base editor are fused via a linker comprising the amino acid sequence SGSETPGTSESATPES (SEQ ID NO: 249), which may also be referred to as the XTEN linker. In some embodiments, a linker comprises the amino acid sequence SGGGS (SEQ ID NO: 355). In some embodiments, the linker is 24 amino acids in length. In some embodiments, the linker comprises the amino acid sequence
- 20 SGGSSGGSSGSETPGTSESATPES (SEQ ID NO: 359). In some embodiments, the linker is 40 amino acids in length. In some embodiments, the linker comprises the amino acid sequence: SGGSSGGSSGSETPGTSESATPESGGSSGGSSGGSSGGGS (SEQ ID NO: 360). In some embodiments, the linker is 64 amino acids in length. In some embodiments, the linker comprises the amino acid sequence:

- 25 SGGSSGGSSGSETPGTSESATPESGGSSGGSSGGSSGGSSGSETPGTSESATPESGGSSGGSS (SEQ ID NO: 361). In some embodiments, the linker is 92 amino acids in length. In some embodiments, the linker comprises the amino acid sequence:
 PGSPAGSPTSTEEGTSESATPESGPGTSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSAPG
 TSTEPSEGSAPGTSESATPESGPGSEPAT (SEQ ID NO: 362).

- 30 In some embodiments, a linker comprises a plurality of proline residues and is 5-21, 5-14, 5-9, 5-7 amino acids in length, *e.g.*, PAPAP (SEQ ID NO: 363), PAPAPA (SEQ ID NO: 364), PAPAPAP (SEQ ID NO: 365), PAPAPAPA (SEQ ID NO: 366), P(AP)₄ (SEQ ID NO: 367), P(AP)₇ (SEQ ID NO: 368), P(AP)₁₀ (SEQ ID NO: 369) (see, *e.g.*, Tan J, Zhang F, Karcher

D, Bock R. Engineering of high-precision base editors for site-specific single nucleotide replacement. Nat Commun. 2019 Jan 25;10(1):439; the entire contents are incorporated herein by reference). Such proline-rich linkers are also termed “rigid” linkers.

In various embodiments, a linker of the disclosure comprises 8, 9, 10, 11, 12, 13, 14, 5 or 15 amino acids. In some cases, the linker comprises a sequence selected from one or more of EGSSSKKEEEEPG (SEQ ID NO: 647), NSISSSNGQK (SEQ ID NO: 648), GEEGEGSGGGGK (SEQ ID NO: 649), EGEGGKESGSSE (SEQ ID NO: 650), GGGGSSKSPGSE (SEQ ID NO: 651), PIGSDQDD (SEQ ID NO: 652), TEKGQVPHGS (SEQ ID NO: 653), ESGEGGGGSEKK (SEQ ID NO: 654), EEGKPKEGEGSG (SEQ ID NO: 655), 10 ASREPKDSS (SEQ ID NO: 656), KQGSEHDE (SEQ ID NO: 657), SESKSEKGSSEK (SEQ ID NO: 658), QYDSGERSDQ (SEQ ID NO: 659), PGANEEIPGQ (SEQ ID NO: 660), NSPTDEK (SEQ ID NO: 661), EGANEEIPGQ (SEQ ID NO: 662), EGEKEKKKSGES (SEQ ID NO: 663), PGRHEEVPGQ (SEQ ID NO: 664), SKHQTEQDD (SEQ ID NO: 665), ESEDDSSGRK (SEQ ID NO: 666), KESEKKESESKS (SEQ ID NO: 667), KGEKGSSIKD (SEQ ID NO: 668), DRSQKQDQDD (SEQ ID NO: 669), GPSSTSSS (SEQ ID NO: 670), GSSGEKEEGEPPS (SEQ ID NO: 671), GEPKSKKSGSGS (SEQ ID NO: 672), SSGEGGKSES GP (SEQ ID NO: 673), SPQPTSSD (SEQ ID NO: 674), EGGSEEEEEESGS (SEQ ID NO: 675), KGPKPKKEESEK (SEQ ID NO: 676), SKSQQFVITYE (SEQ ID NO: 677), TGNSKYQTGK (SEQ ID NO: 678), PQPIPTNPT (SEQ ID NO: 679), ANAHSDISTG (SEQ ID NO: 680), KSQQTEDQSK (SEQ ID NO: 681), QSQDQKQKEH (SEQ ID NO: 682), 20 NQQRPSDD (SEQ ID NO: 683), TTKDTSPKPQ (SEQ ID NO: 684), EGKDNQQTGE (SEQ ID NO: 685), or EPQPDSSSE (SEQ ID NO: 686).

Nucleic Acid Programmable DNA Binding Proteins with Guide RNAs

25 Provided herein are compositions and methods for base editing in cells. Further provided herein are compositions comprising a guide polynucleotide sequence, *e.g.*, a guide RNA sequence, or a combination of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more guide RNAs as provided herein. In some embodiments, a composition for base editing as provided herein further comprises a polynucleotide that encodes a base editor, *e.g.*, 30 a C-base editor or an A-base editor. For example, a composition for base editing may comprise a mRNA sequence encoding a BE, a BE4, an ABE, and a combination of one or more guide RNAs as provided. A composition for base editing may comprise a base editor polypeptide and a combination of one or more of any guide RNAs provided herein. Such a

composition may be used to effect base editing in a cell through different delivery approaches, for example, electroporation, nucleofection, viral transduction or transfection. In some embodiments, the composition for base editing comprises an mRNA sequence that encodes a base editor and a combination of one or more guide RNA sequences provided
5 herein for electroporation.

Some aspects of this disclosure provide systems comprising any of the fusion proteins or complexes provided herein, and a guide RNA bound to a nucleic acid programmable DNA binding protein (napDNAbp) domain (*e.g.*, a Cas9 (*e.g.*, a dCas9, a nuclease active Cas9, or a Cas9 nickase) or Cas12) of the fusion protein or complex. These complexes are also termed
10 ribonucleoproteins (RNPs). In some embodiments, the guide nucleic acid (*e.g.*, guide RNA) is from 15-100 nucleotides long and comprises a sequence of at least 10 contiguous nucleotides that is complementary to a target sequence. In some embodiments, the target sequence is a DNA sequence. In some embodiments, the target sequence is an RNA sequence. In some embodiments, the target sequence is a sequence in the genome of a
15 bacteria, yeast, fungi, insect, plant, or animal. In some embodiments, the target sequence is a sequence in the genome of a human. In some embodiments, the 3' end of the target sequence is immediately adjacent to a canonical PAM sequence (NGG). In some embodiments, the 3' end of the target sequence is immediately adjacent to a non-canonical PAM sequence (*e.g.*, a sequence listed in **Table 3** or 5'-NAA-3'). In some embodiments, the guide nucleic acid (*e.g.*,
20 guide RNA) is complementary to a sequence in a gene of interest (*e.g.*, a gene associated with a disease or disorder).

Some aspects of this disclosure provide methods of using the fusion proteins, or complexes provided herein. For example, some aspects of this disclosure provide methods comprising contacting a DNA molecule with any of the fusion proteins or complexes
25 provided herein, and with at least one guide RNA, wherein the guide RNA is about 15-100 nucleotides long and comprises a sequence of at least 10 contiguous nucleotides that is complementary to a target sequence.

The domains of the base editor disclosed herein can be arranged in any order.

A defined target region can be a deamination window. A deamination window can be
30 the defined region in which a base editor acts upon and deaminates a target nucleotide. In some embodiments, the deamination window is within a 2, 3, 4, 5, 6, 7, 8, 9, or 10 base regions. In some embodiments, the deamination window is 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 bases upstream of the PAM.

The base editors of the present disclosure can comprise any domain, feature or amino acid sequence which facilitates the editing of a target polynucleotide sequence.

Methods of Using Fusion Proteins or Complexes Comprising a Cytidine or Adenosine

5 *Deaminase and a Cas9 Domain*

Some aspects of this disclosure provide methods of using the fusion proteins, or complexes provided herein. For example, some aspects of this disclosure provide methods comprising contacting a DNA molecule with any of the fusion proteins or complexes provided herein, and with at least one guide RNA described herein.

10 In some embodiments, a fusion protein or complex of the disclosure is used for editing a target gene of interest. In particular, a cytidine deaminase or adenosine deaminase nucleobase editor described herein is capable of making multiple mutations within a target sequence. These mutations may affect the function of the target. For example, when a cytidine deaminase or adenosine deaminase nucleobase editor is used to target a regulatory
15 region the function of the regulatory region is altered and the expression of the downstream protein is reduced or eliminated.

Base Editor Efficiency

In some embodiments, the purpose of the methods provided herein is to alter a gene
20 and/or gene product via gene editing. The nucleobase editing proteins provided herein can be used for gene editing-based human therapeutics in vitro or in vivo. It will be understood by the skilled artisan that the nucleobase editing proteins provided herein, *e.g.*, the fusion proteins or complexes comprising a polynucleotide programmable nucleotide binding domain (*e.g.*, Cas9) and a nucleobase editing domain (*e.g.*, an adenosine deaminase domain or a
25 cytidine deaminase domain) can be used to edit a nucleotide from A to G or C to T.

Advantageously, base editing systems as provided herein provide genome editing without generating double-strand DNA breaks, without requiring a donor DNA template, and without inducing an excess of stochastic insertions and deletions as CRISPR may do. In some
30 embodiments, the present disclosure provides base editors that efficiently generate an intended mutation, such as a STOP codon, in a nucleic acid (*e.g.*, a nucleic acid within a genome of a subject) without generating a significant number of unintended mutations, such as unintended point mutations.

The base editors of the disclosure advantageously modify a specific nucleotide base encoding a protein without generating a significant proportion of indels (i.e., insertions or deletions). Such indels can lead to frame shift mutations within a coding region of a gene.

In some embodiments, the base editors provided herein are capable of generating a ratio of intended mutations to indels (*i.e.*, intended point mutations:unintended point mutations) that is greater than 1:1. In some embodiments, the base editors provided herein are capable of generating a ratio of intended mutations to indels that is at least 1.5:1, at least 2:1, at least 2.5:1, at least 3:1, at least 3.5:1, at least 4:1, at least 4.5:1, at least 5:1, at least 5.5:1, at least 6:1, at least 6.5:1, at least 7:1, at least 7.5:1, at least 8:1, at least 10:1, at least 12:1, at least 15:1, at least 20:1, at least 25:1, at least 30:1, at least 40:1, at least 50:1, at least 100:1, at least 200:1, at least 300:1, at least 400:1, at least 500:1, at least 600:1, at least 700:1, at least 800:1, at least 900:1, or at least 1000:1, or more. The number of intended mutations and indels may be determined using any suitable method.

In some embodiments, the base editors provided herein can limit formation of indels in a region of a nucleic acid. In some embodiments, the region is at a nucleotide targeted by a base editor or a region within 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides of a nucleotide targeted by a base editor. In some embodiments, any of the base editors provided herein can limit the formation of indels at a region of a nucleic acid to less than 1%, less than 1.5%, less than 2%, less than 2.5%, less than 3%, less than 3.5%, less than 4%, less than 4.5%, less than 5%, less than 6%, less than 7%, less than 8%, less than 9%, less than 10%, less than 12%, less than 15%, or less than 20%.

Base editing is often referred to as a “modification”, such as, a genetic modification, a gene modification and modification of the nucleic acid sequence and is clearly understandable based on the context that the modification is a base editing modification. A base editing modification is therefore a modification at the nucleotide base level, for example as a result of the deaminase activity discussed throughout the disclosure, which then results in a change in the gene sequence and may affect the gene product.

In some embodiments, the modification, *e.g.*, single base edit results in about or at least about a 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or 100% reduction, or reduction to an undetectable level, of the gene targeted expression.

The disclosure provides adenosine deaminase variants (*e.g.*, ABE8 variants) that have increased efficiency and specificity. In particular, the adenosine deaminase variants described

herein are more likely to edit a desired base within a polynucleotide and are less likely to edit bases that are not intended to be altered (*e.g.*, “bystanders”).

In some embodiments, any of the base editing system comprising one of the ABE8 base editor variants described herein has reduced bystander editing or mutations by at least
5 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% compared to a base editor system comprising an ABE7 base editor, *e.g.*, ABE7.10.

In some embodiments, any of the ABE8 base editor variants described herein has higher base editing efficiency compared to the ABE7 base editors. In some embodiments, any
10 of the ABE8 base editor variants described herein have at least 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, 100%, 105%, 110%, 115%, 120%, 125%, 130%, 135%, 140%, 145%, 150%, 155%, 160%, 165%, 170%, 175%, 180%, 185%, 190%, 195%, 200%, 210%, 220%, 230%, 240%, 250%, 260%, 270%, 280%, 290%, 300%, 310%,
15 320%, 330%, 340%, 350%, 360%, 370%, 380%, 390%, 400%, 450%, or 500% higher base editing efficiency compared to an ABE7 base editor, *e.g.*, ABE7.10.

The ABE8 base editor variants described herein may be delivered to a host cell via a plasmid, a vector, a LNP complex, or an mRNA. In some embodiments, any of the ABE8 base editor variants described herein is delivered to a host cell as an mRNA.

20 In some embodiments, the method described herein, for example, the base editing methods has minimum to no off-target effects. In some embodiments, the method described herein, for example, the base editing methods, has minimal to no chromosomal translocations.

In some embodiments, the base editing method described herein results in about 91%,
25 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% of a cell population that have been successfully edited.

In some embodiments, the percent of viable cells in a cell population following a base editing intervention is greater than at least 60%, 70%, 80%, or 90% of the starting cell population at the time of the base editing event. In some embodiments, the percent of viable
30 cells in a cell population following editing is about 70%. In some embodiments, the percent of viable cells in a cell population following editing is about 75%. In some embodiments, the percent of viable cells in a cell population following editing is about 80%. In some embodiments, the percent of viable cells in a cell population as described above is about 85%. In some embodiments, the percent of viable cells in a cell population as described

above is about 90%, or about 91%, 92%, 93%, 94% 95%, 96%, 97%, 98%, 99%, or 100% of the cells in the population at the time of the base editing event.

In embodiments, the cell population is a population of cells contacted with a base editor, complex, or base editor system of the present disclosure.

5 The number of intended mutations and indels can be determined using any suitable method, for example, as described in International PCT Application Nos. PCT/US2017/045381 (WO2018/027078) and PCT/US2016/058344 (WO2017/070632); Komor, A.C., *et al.*, “Programmable editing of a target base in genomic DNA without double-stranded DNA cleavage” *Nature* 533, 420-424 (2016); Gaudelli, N.M., *et al.*,
10 “Programmable base editing of A•T to G•C in genomic DNA without DNA cleavage” *Nature* 551, 464-471 (2017); and Komor, A.C., *et al.*, “Improved base excision repair inhibition and bacteriophage Mu Gam protein yields C:G-to-T:A base editors with higher efficiency and product purity” *Science Advances* 3:eaa04774 (2017); the entire contents of which are hereby incorporated by reference.

15 In some embodiments, to calculate indel frequencies, sequencing reads are scanned for exact matches to two 10-bp sequences that flank both sides of a window in which indels can occur. If no exact matches are located, the read is excluded from analysis. If the length of this indel window exactly matches the reference sequence the read is classified as not containing an indel. If the indel window is two or more bases longer or shorter than the
20 reference sequence, then the sequencing read is classified as an insertion or deletion, respectively. In some embodiments, the base editors provided herein can limit formation of indels in a region of a nucleic acid. In some embodiments, the region is at a nucleotide targeted by a base editor or a region within 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides of a nucleotide targeted by a base editor.

25

Multiplex Editing

 In some embodiments, the base editor system provided herein is capable of multiplex editing of a plurality of nucleobase pairs in one or more genes or polynucleotide sequences. In some embodiments, the plurality of nucleobase pairs is located in the same gene or in one
30 or more genes, wherein at least one gene is located in a different locus. In some embodiments, the multiplex editing comprises one or more guide polynucleotides. In some embodiments, the multiplex editing comprises one or more base editor systems. In some embodiments, the multiplex editing comprises one or more base editor systems with a single guide polynucleotide or a plurality of guide polynucleotides. In some embodiments, the

5 multiplex editing comprises one or more guide polynucleotides with a single base editor system. It should be appreciated that the characteristics of the multiplex editing using any of the base editors as described herein can be applied to any combination of methods using any base editor provided herein. It should also be appreciated that the multiplex editing using any of the base editors as described herein can comprise a sequential editing of a plurality of nucleobase pairs.

In some embodiments, the base editor system capable of multiplex editing of a plurality of nucleobase pairs in one or more genes comprises one of ABE7, ABE8, and/or ABE9 base editors.

10

Expression of Fusion Proteins or Complexes in a Host Cell

Fusion proteins or complexes of the disclosure comprising a deaminase may be expressed in virtually any host cell of interest, including but not limited to bacteria, yeast, fungi, insects, plants, and animal cells using routine methods known to the skilled artisan. For example, a DNA encoding an adenosine deaminase of the disclosure can be cloned by designing suitable primers for the upstream and downstream of CDS based on the cDNA sequence. The cloned DNA may be directly, or after digestion with a restriction enzyme when desired, or after addition of a suitable linker and/or a nuclear localization signal, ligated with a DNA encoding one or more additional components of a base editing system. The base editing system is translated in a host cell to form a complex.

20 A polynucleotide encoding a polypeptide described herein can be obtained by chemically synthesizing the polynucleotide, or by connecting synthesized partly overlapping oligo short chains by utilizing the PCR method and the Gibson Assembly method to construct a polynucleotide (e.g., DNA) encoding the full length thereof. The advantage of constructing a full-length polynucleotide by chemical synthesis or a combination of PCR method or Gibson Assembly method is that the codons to be used can be selected in according to the host into which the polynucleotide is to be introduced. In the expression from a heterologous DNA molecule, the protein expression level is expected to increase by converting the DNA sequence thereof to a codon highly frequently used in the host organism. Codon use data for a host cell (e.g., codon use data available at kazusa.or.jp/codon/index.html) can be used to guide codon optimization for a polynucleotide sequence encoding a polypeptide. Codons having low use frequency in the host may be converted to a codon coding the same amino acid and having high use frequency.

An expression vector containing a polynucleotide encoding a nucleic acid sequence-recognizing module and/or a nucleic acid base converting enzyme can be produced, for example, by linking the DNA to the downstream of a promoter in a suitable expression vector.

5 As the expression vector, *Escherichia coli*-derived plasmids (e.g., pBR322, pBR325, pUC12, pUC13); *Bacillus subtilis*-derived plasmids (e.g., pUB110, pTP5, pC194); yeast-derived plasmids (e.g., pSH19, pSH15); insect cell expression plasmids (e.g., pFast-Bac); animal cell expression plasmids (e.g., pA1-11, pXT1, pRc/CMV, pRc/RSV, pcDNAI/Neo); bacteriophages such as .lambda phage and the like; insect virus vectors such as baculovirus
10 and the like (e.g., BmNPV, AcNPV); animal virus vectors such as retrovirus, vaccinia virus, adenovirus and the like, and the like are used.

Regarding the promoter to be used, any promoter appropriate for a host to be used for gene expression can be used. In a method using double-stranded breaks, since the survival rate of the host cell sometimes reduces markedly due to the toxicity, it is desirable to increase
15 the number of cells by the start of the induction by using an inductive promoter. However, since sufficient cell proliferation can also be afforded by expressing the nucleic acid-modifying enzyme complex of the present disclosure, a constitutive promoter can be used without limitation.

For example, when the host is an animal cell, an SR.alpha. promoter, SV40 promoter,
20 LTR promoter, cytomegalovirus (CMV) promoter, Rous sarcoma virus (RSV) promoter, Moloney mouse leukemia virus (MoMuLV), LTR, herpes simplex virus thymidine kinase (HSV-TK) promoter, and the like can be used. Of these, CMV promoter, SR.alpha. promoter and the like may be used.

Expression vectors for use in the present disclosure, besides those mentioned above,
25 can comprise an enhancer, a splicing signal, a terminator, a polyA addition signal, a selection marker such as drug resistance gene, an auxotrophic complementary gene and the like, a replication origin, and the like can be used.

An RNA encoding a protein domain described herein can be prepared by, for example, *in vitro* transcription of a nucleic acid sequence encoding any of the fusion proteins
30 or complexes disclosed herein.

A fusion protein or complex of the disclosure can be intracellularly expressed by introducing into the cell an expression vector comprising a nucleic acid sequence encoding the fusion protein or complex.

An expression vector can be introduced by a known method (*e.g.*, the lysozyme method, the competent method, the PEG method, the CaCl₂ coprecipitation method, electroporation, microinjection, particle gun method, lipofection, *Agrobacterium*-mediated delivery, etc.) according to the kind of the host.

- 5 A vector can be introduced into an animal cell according to the methods described in, for example, Cell Engineering additional volume 8, New Cell Engineering Experiment Protocol, 263-267 (1995) (published by Shujunsha), and Virology, 52, 456 (1973).

A cell comprising a vector can be cultured according to a known method according to the kind of the host.

- 10 As a medium for culturing an animal cell, for example, minimum essential medium (MEM) containing about 5 to about 20% of fetal bovine serum [Science, 122, 501 (1952)], Dulbecco's modified Eagle medium (DMEM) [Virology, 8, 396 (1959)], RPMI 1640 medium [The Journal of the American Medical Association, 199, 519 (1967)], 199 medium [Proceeding of the Society for the Biological Medicine, 73, 1 (1950)] and the like are used.

- 15 The pH of the medium may be between about 6 to about 8. The culture is performed at generally about 30°C. to about 40°C. Where necessary, aeration and stirring may be performed.

- When a higher eukaryotic cell, such as animal cell, insect cell, plant cell and the like is used as a host cell, a polynucleotide encoding a base editing system of the present disclosure (*e.g.*, comprising an adenosine deaminase variant) is introduced into a host cell under the regulation of an inducible promoter (*e.g.*, metallothionein promoter (induced by heavy metal ion), heat shock protein promoter (induced by heat shock), Tet-ON/Tet-OFF system promoter (induced by addition or removal of tetracycline or a derivative thereof), steroid-responsive promoter (induced by steroid hormone or a derivative thereof) etc.), the induction substance is added to the medium (or removed from the medium) at an appropriate stage to induce expression of the nucleic acid-modifying enzyme complex, culture is performed for a given period to carry out a base editing and, introduction of a mutation into a target gene, transient expression of the base editing system can be realized.

- 25 Alternatively, an inductive promoter can also be utilized as a vector removal mechanism when higher eukaryotic cells, such as animal cell, insect cell, plant cell and the like are used as a host cell. That is, a vector is mounted with a replication origin that functions in a host cell, and a nucleic acid encoding a protein necessary for replication (*e.g.*, SV40 on and large T antigen, oriP and EBNA-1 etc. for animal cells), of the expression of the nucleic acid encoding the protein is regulated by the above-mentioned inducible promoter. As

a result, while the vector is autonomously replicable in the presence of an induction substance, when the induction substance is removed, autonomous replication is not available, and the vector naturally falls off along with cell division (autonomous replication is not possible by the addition of tetracycline and doxycycline in Tet-OFF system vector).

5

REDUCING EXPRESSION OF TARGET GENES IN CELLS

In some embodiments, provided herein is a cell (e.g., cell from the liver, eye, and/or a central nervous system or component thereof) with at least one modification in an endogenous gene or one or more regulatory elements thereof. Provided herein are also

10 methods, base editors, base editor systems, guide RNAs, and compositions for modifying the cell. In some embodiments, the cell may comprise a further modification in at least one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty or more endogenous genes or regulatory elements thereof. In some embodiments, the at least one modification is a single nucleobase

15 modification. In some embodiments, the at least one modification is generated by base editing. The base editing may be positioned at any suitable position of the gene, or in a regulatory element of the gene. Thus, it may be appreciated that a single base editing at a start codon, for example, can completely abolish the expression of the gene. In some embodiments, the base editing may be performed at a site within an exon. In some

20 embodiments, the base editing may be performed at a site on more than one exons. In some embodiments, the base editing may be performed at any exon of the multiple exons in a gene. In some embodiments, base editing may introduce a premature STOP codon into an exon, resulting in either lack of a translated product or in a truncated that may be misfolded and thereby eliminated by degradation, or may produce an unstable mRNA that is readily

25 degraded. In some embodiments, the cell is a hepatocyte, and/or a cell from the liver, eye, and/or a central nervous system or component thereof.

In some embodiments, the gene is a factor B polynucleotide.

In some embodiments, the editing of the endogenous gene reduces expression of the gene. In some embodiments, the editing of the endogenous gene reduces expression of the

30 gene by at least 50% as compared to a control cell without the modification. In some embodiments, the editing of the endogenous gene reduces expression of the gene by at least 60% as compared to a control cell without the modification. In some embodiments, the editing of the endogenous gene reduces expression of the gene by at least 70% as compared to a control cell without the modification. In some embodiments, the editing of the

endogenous gene reduces expression of the gene by at least 80% as compared to a control cell without the modification. In some embodiments, the editing of the endogenous gene reduces expression of the gene by at least 90% as compared to a control cell without the modification. In some embodiments, the editing of the endogenous gene reduces expression of the gene by
 5 at least 100% as compared to a control cell without the modification. In some embodiments, the editing of the endogenous gene eliminates gene expression.

In some embodiments, base editing may be performed on an intron. For example, base editing may be performed on an intron. In some embodiments, the base editing may be performed at a site within an intron. In some embodiments, the base editing may be
 10 performed at sites in one or more introns. In some embodiments, the base editing may be performed at any intron of the multiple introns in a gene. In some embodiments, one or more base edits may be performed on an exon, an intron, or any combination of exons and introns.

In some embodiments, the modification or base edit may be within a promoter site. In some embodiments, the base edit may be introduced within an alternative promoter site. In
 15 some embodiments, the base edit may be in a 5' regulatory element, such as an enhancer. In some embodiment, base editing may be introduced to disrupt the binding site of a nucleic acid binding protein. Exemplary nucleic acid binding proteins may be a polymerase, nuclease, gyrase, topoisomerase, methylase or methyl transferase, transcription factors, enhancer, PABP, zinc finger proteins, among many others.

In some embodiments, base editing may be used for splice disruption to silence target protein expression. In some embodiments, base editing may generate a splice acceptor-splice donor (SA-SD) site. Targeted base editing generating a SA-SD, or at a SA-SD site can result in reduced expression of a gene. In some embodiments, base editors (*e.g.*, ABE, CBE, or CAGE)
 20 (CAGE) are used to target dinucleotide motifs that constitute splice acceptor and splice donor sites, which are the first and last two nucleotides of each intron. In some embodiments, splice disruption is achieved with an adenosine base editor (ABE). In some embodiments, splice disruption is achieved with a cytidine base editor (CBE). In some embodiments, base editors (*e.g.*, ABE, CBE, or CAGE) are used to edit exons by creating STOP codons.

In some embodiments, the modification generates a premature stop codon in the
 30 endogenous genes. In some embodiments, the STOP codon silences target protein expression. In some embodiments, the modification is a single base modification. In some embodiments, the modification is generated by base editing. The premature stop codon may be generated in an exon, an intron, or an untranslated region. In some embodiments, base editing may be used to introduce more than one STOP codon, in one or more alternative

reading frames. In some embodiments, the stop codon is generated by a adenosine base editor (ABE). In some embodiments, the stop codon is generated by a cytidine base editor (CBE).

In some embodiments, the CBE generates any one of the following edits (shown in underlined font) to generate a STOP codon: CAG→TAG; CAA→TAA; CGA→TGA;

5 TGG→TGA; TGG→TAG; or TGG→TAA.

In some embodiments, modification/base edits may be introduced at a 3'-UTR, for example, in a poly adenylation (poly-A) site. In some embodiments, base editing may be performed on a 5'-UTR region.

10 **DELIVERY SYSTEMS**

Nucleic Acid-Based Delivery of Base Editor Systems

Nucleic acid molecules encoding a base editor system according to the present disclosure can be administered to subjects or delivered into cells *in vitro* or *in vivo* by art-known methods or as described herein. For example, a base editor system comprising a
15 deaminase (*e.g.*, cytidine or adenine deaminase) can be delivered by vectors (*e.g.*, viral or non-viral vectors), or by naked DNA, DNA complexes, lipid nanoparticles, or a combination of the aforementioned compositions. A base editor system may be delivered to a cell using any methods available in the art including, but not limited to, physical methods (*e.g.*, electroporation, particle gun, calcium phosphate transfection), viral methods, non-viral
20 methods (*e.g.*, liposomes, cationic methods, lipid nanoparticles, polymeric nanoparticles), or biological non-viral methods (*e.g.*, attenuated bacterial, engineered bacteriophages, mammalian virus-like particles, biological liposomes, erythrocyte ghosts, exosomes).

Nanoparticles, which can be organic or inorganic, are useful for delivering a base editor system or component thereof. Nanoparticles are well known in the art and any suitable
25 nanoparticle can be used to deliver a base editor system or component thereof, or a nucleic acid molecule encoding such components. In one example, organic (*e.g.*, lipid and/or polymer) nanoparticles are suitable for use as delivery vehicles in certain embodiments of this disclosure. Non-limiting examples of lipid nanoparticles suitable for use in the methods of the present disclosure include those described in International Patent Application
30 Publications No. WO2022140239, WO2022140252, WO2022140238, WO2022159421, WO2022159472, WO2022159475, WO2022159463, WO2021113365, WO2024019936, and WO2021141969, the disclosures of each of which is incorporated herein by reference in its entirety for all purposes.

Viral Vectors

A base editor described herein can be delivered with a viral vector. In some embodiments, a base editor disclosed herein can be encoded on a nucleic acid that is
5 contained in a viral vector. In some embodiments, one or more components of the base editor system can be encoded on one or more viral vectors.

Viral vectors can include lentivirus (*e.g.*, HIV and FIV-based vectors), Adenovirus (*e.g.*, AD100), Retrovirus (*e.g.*, Maloney murine leukemia virus, MML-V), herpesvirus vectors (*e.g.*, HSV-2), rabies virus (see, *e.g.*, U.S. Patent Application Publication No. US
10 2022/0290164 A1, the disclosure of which is incorporated herein by reference in its entirety for all purposes), and Adeno-associated viruses (AAVs), or other plasmid or viral vector types, in particular, using formulations and doses from, for example, U.S. Patent No. 8,454,972 (formulations, doses for adenovirus), U.S. Patent No. 8,404,658 (formulations, doses for AAV) and U.S. Patent No. 5,846,946 (formulations, doses for DNA plasmids) and
15 from clinical trials and publications regarding the clinical trials involving lentivirus, AAV and adenovirus. For example, for AAV, the route of administration, formulation and dose can be as in U.S. Patent No. 8,454,972 and as in clinical trials involving AAV. For Adenovirus, the route of administration, formulation and dose can be as in U.S. Patent No. 8,404,658 and as in clinical trials involving adenovirus. For plasmid delivery, the route of administration,
20 formulation and dose can be as in U.S. Patent No. 5,846,946 and as in clinical studies involving plasmids. Doses can be based on or extrapolated to an average 70 kg individual (*e.g.*, a male adult human), and can be adjusted for patients, subjects, mammals of different weight and species. Frequency of administration is within the ambit of the medical or veterinary practitioner (*e.g.*, physician, veterinarian), depending on usual factors including
25 the age, sex, general health, other conditions of the patient or subject and the particular condition or symptoms being addressed. The viral vectors can be injected into the tissue of interest. For cell-type specific base editing, the expression of the base editor and optional guide nucleic acid can be driven by a cell-type specific promoter.

Viral vectors can be selected based on the application. For example, for in vivo gene
30 delivery, AAV can be advantageous over other viral vectors. In some embodiments, AAV allows low toxicity, which can be due to the purification method not requiring ultra-centrifugation of cell particles that can activate the immune response. In some embodiments, AAV allows low probability of causing insertional mutagenesis because it doesn't integrate into the host genome. Adenoviruses are commonly used as vaccines because of the strong

immunogenic response they induce. Packaging capacity of the viral vectors can limit the size of the base editor that can be packaged into the vector.

AAV has a packaging capacity of about 4.5 Kb or 4.75 Kb including two 145 base inverted terminal repeats (ITRs). This means disclosed base editor as well as a promoter and transcription terminator can fit into a single viral vector. Constructs larger than 4.5 or 4.75 Kb can lead to significantly reduced virus production. For example, SpCas9 is quite large, the gene itself is over 4.1 Kb, which makes it difficult for packing into AAV. Therefore, embodiments of the present disclosure include utilizing a disclosed base editor which is shorter in length than conventional base editors. In some examples, the base editors are less than 4 kb. Disclosed base editors can be less than 4.5 kb, 4.4 kb, 4.3 kb, 4.2 kb, 4.1 kb, 4 kb, 3.9 kb, 3.8 kb, 3.7 kb, 3.6 kb, 3.5 kb, 3.4 kb, 3.3 kb, 3.2 kb, 3.1 kb, 3 kb, 2.9 kb, 2.8 kb, 2.7 kb, 2.6 kb, 2.5 kb, 2 kb, or 1.5 kb. In some embodiments, the disclosed base editors are 4.5 kb or less in length.

An AAV can be AAV1, AAV2, AAV5, AAV6, AAV9, PHP.EB, PHP.B, AAV.CAP-B10, AAV, CAP-B22, AAV-rh10, a PAL family AAV, or any combination thereof. In embodiments, the AAV is capable of crossing the blood-brain barrier (see, e.g., those AAV vectors disclosed in Liu, *et al.* "Crossing the blood-brain barrier with AAV vectors," *Metabolic Brain Disease*, 36:45-52 (2021), the disclosure of which is incorporated herein by reference in its entirety for all purposes). One can select the type of AAV with regard to the cells to be targeted; e.g., one can select AAV serotypes 1, 2, 5 or a hybrid capsid AAV1, AAV2, AAV5 or any combination thereof for targeting brain or neuronal cells; and one can select AAV4 for targeting cardiac tissue. AAV8 is useful for delivery to the liver. A tabulation of certain AAV serotypes as to these cells can be found in Grimm, D. et al, J. Virol. 82: 5887-5911 (2008)).

In some embodiments, the AAV vector contains a PAL family AAV capsid (see, Stanton, A., *et al. Med* 4:31-50 (2023) (doi: doi.org/10.1016/j.medj.2022.11.002), the disclosure of which is incorporated herein by reference in its entirety for all purposes). In some cases, the AAV PAL family AAV capsid contains the below AAV9 VP1 capsid amino acid sequence (UniProt Accession No. Q6JC40) with one of the 7-mers listed in **Table 8** below inserted between amino acid positions Q588 and A589, which are shown in bold in the below sequence. In some embodiments, the AAV PAL family AAV capsid contains the below AAV9 VP1 capsid amino acid sequence with the amino acid alterations A587D and Q588G and one of the 7-mers listed in **Table 8** inserted between amino acid positions G588 and A589.

>AAV9 VP1 capsid amino acid sequence: tr|Q6JC40|Q6JC40_9VIRU Capsid protein VP1
OS=Adeno-associated virus 9 OX=235455 GN=cap PE=1 SV=1
MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPNGGLDKG
5 EPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADADEFQERLKEDTSFGGNLGRAVFAQKKR
LLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAKKRLNFGQTDGDTESVPDPQ
PIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSSSGNWHCDSQWLGDREVITTTSTRTWA
LPTYNNHLYKQISNSTSGGSSNDNAYFGYSTPWGYFDFNRFHCHFSPRDWQRLINNNWGFRL
KRLNFKLFNIQVKEVTDNNGVKTIANNLSTVQVFTDSDYQLPYVLGSAHEGCLPPFPADV
10 MIPQYGYLTLNDGSQAVGRSSFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSQSLDR
LMNPLIDQYLYYLSKTINGSGQNQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQN
NNSEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVDADKV
MITNEEEIKTTNPVATESYGQVATNHQSAQAQAQTGWVQNQGILPGMVWQDRDVYLQGPIWA
KIPHTDGNFHPSPLMGGFGMKHPPQILIKNTPVPADPPTAFNKDKLNSFITQYSTGQVSVE
15 IEWELQKENSKRWNPEIQYTSNYYKSNNVEFAVNTGVYSEPRPIGTRYLTRNL (SEQ ID
NO: 3559)

Table 8. PAL family AAV vector inserts.

7-mer	SEQ ID NO
RSVGSVY	3531
KTVGTVY	3532
RYLGDAS	3533
WVLPSGG	3534
VTVGSIY	3535
VRGSSIL	3536
REQQKLW	3537
ASNPGRW	3538
SLDKPFK	3539
TLAVPFK	3540
WTLESGH	3541
REQKKLW	3542
PTQGTVR	3543
PTQGTFR	3544
PSQGTLR	3545
NLGAALS	3546
PKPSHGE	3547
PTPGTLR	3548
PTQGTLR	3549
QDGPAVK	3550
PNQGTLR	3551
ESLAGVR	3552
TDALTTK	3553

7-mer	SEQ ID NO
TDAGDGK	3554
MTGISIV	3555
NGYTEGR	3556
SLVTSST	3557
PTQGTIR	3558

In some embodiments, lentiviral vectors are used to transduce a cell of interest with a polynucleotide encoding a base editor or base editor system as provided herein. Lentiviruses are complex retroviruses that have the ability to infect and express their genes in both mitotic and post-mitotic cells. The most commonly known lentivirus is the human immunodeficiency virus (HIV), which uses the envelope glycoproteins of other viruses to target a broad range of cell types.

In another embodiment, minimal non-primate lentiviral vectors based on the equine infectious anemia virus (EIAV) are also contemplated. In another embodiment, RetinoStat®, an equine infectious anemia virus-based lentiviral gene therapy vector that expresses angiostatic proteins endostatin and angiostatin that is contemplated to be delivered via a subretinal injection. In another embodiment, use of self-inactivating lentiviral vectors are contemplated.

Any RNA of the systems, for example a guide RNA or a base editor-encoding mRNA, can be delivered in the form of RNA. Base editor-encoding mRNA can be generated using in vitro transcription. For example, nuclease mRNA can be synthesized using a PCR cassette containing the following elements: T7 promoter, optional kozak sequence (GCCACC), nuclease sequence, and 3' UTR such as a 3' UTR from beta globin-polyA tail. The cassette can be used for transcription by T7 polymerase. Guide polynucleotides (e.g., gRNA) can also be transcribed using in vitro transcription from a cassette containing a T7 promoter, followed by the sequence “GG”, and guide polynucleotide sequence.

Non-Viral Platforms for Gene Transfer

Non-viral platforms for introducing a heterologous polynucleotide into a cell of interest are known in the art.

For example, the disclosure provides a method of inserting a heterologous polynucleotide into the genome of a cell using a Cas9 or Cas12 (e.g., Cas12b) ribonucleoprotein complex (RNP)-DNA template complex where an RNP including a Cas9 or Cas12 nuclease domain and a guide RNA, wherein the guide RNA specifically hybridizes to a target region of the genome of the cell, and wherein the Cas nuclease domain cleaves the

target region to create an insertion site in the genome of the cell. A DNA template is then used to introduce a heterologous polynucleotide. In embodiments, the DNA template is a double-stranded or single-stranded DNA template, wherein the size of the DNA template is about 200 nucleotides or is greater than about 200 nucleotides, wherein the 5' and 3' ends of the DNA template comprise nucleotide sequences that are homologous to genomic sequences flanking the insertion site. In some embodiments, the DNA template is a single-stranded circular DNA template. In embodiments, the molar ratio of RNP to DNA template in the complex is from about 3:1 to about 100:1.

In some embodiments, the DNA template is a linear DNA template. In some examples, the DNA template is a single-stranded DNA template. In certain embodiments, the single-stranded DNA template is a pure single-stranded DNA template. In some embodiments, the single stranded DNA template is a single-stranded oligodeoxynucleotide (ssODN).

In other embodiments, a single-stranded DNA (ssDNA) can produce efficient homology-directed repair (HDR) with minimal off-target integration. In one embodiment, an ssDNA phage is used to efficiently and inexpensively produce long circular ssDNA (cssDNA) donors. These cssDNA donors serve as efficient HDR templates when used with Cas9 or Cas12 (e.g., Cas12a, Cas12b), with integration frequencies superior to linear ssDNA (lssDNA) donors.

In some embodiments, a heterologous polynucleotide may be inserted into the genome of a cell using a transposable element such as a transposon, as described, for example, in Tipanee, *et al. Human Gene Therapy*, Nov. 2017, 1087-1104, DOI: 10.1089/hum.2017.128. Transposable elements are divided into two categories: retrotransposons and DNA transposons. Transposable elements can alter the genome of the host cells through insertions, duplications, deletions, and translocations. Retrotransposons are described as mobile elements that employ an RNA intermediate that is first reverse transcribed into a complementary single-stranded (c) DNA strand by a reverse transcriptase encoded by the retrotransposon. Subsequently, the single-stranded DNA is converted into a double-stranded DNA that then integrates into the host genome. This so-called "replicative mechanism" yields several new copies of retrotransposons expanding throughout the target genome over evolutionary time. Retrotransposons are categorized into many subtypes according to the DNA sequences of the long terminal repeats and its open reading frames. Retrotransposons were employed to enable transgene integration into the target cell DNA, in some cases relying on adenoviral delivery. Alternatively, DNA transposons

translocate via a “non-replicative mechanism,” whereby two Terminal Inverted Repeats (TIRs) are recognized and cleaved by a transposase enzyme, releasing the cognate DNA transposons with free DNA ends. The excised DNA transposons then integrate into a new genomic region where target sites are recognized and cut by the same transposase. This cut-and-paste mechanism usually duplicates DNA target sites upon insertion, leaving target site duplications (TSDs). Non-limiting examples of transposons include the *Sleeping Beauty* (SB) transposon, the *piggyBac* (PB) transposon, and *Tol2* transposable elements.

Inteins

Inteins (intervening protein) are auto-processing domains found in a variety of diverse organisms, which carry out a process known as protein splicing.

Non-limiting examples of inteins include any intein or intein-pair known in the art, which include a synthetic intein based on the dnaE intein, the Cfa-N (e.g., split intein-N) and Cfa-C (e.g., split intein-C) intein pair, has been described (e.g., in Stevens et al., J Am Chem Soc. 2016 Feb. 24; 138(7):2162-5, incorporated herein by reference), and DnaE. Non-limiting examples of pairs of inteins that may be used in accordance with the present disclosure include: Cfa DnaE intein, Ssp GyrB intein, Ssp DnaX intein, Ter DnaE3 intein, Ter ThyX intein, Rma DnaB intein and Cne Prp8 intein (e.g., as described in U.S. Patent No. 8,394,604, incorporated herein by reference). Exemplary nucleotide and amino acid sequences of inteins are provided in the Sequence Listing at SEQ ID NOs: 370-377 and 389-424. Inteins suitable for use in embodiments of the present disclosure and methods for use thereof are described in U.S. Patent No. 10,526,401, International Patent Application Publication No. WO 2013/045632, WO 2024/073385, or WO 2020/051561, and in U.S. Patent Application Publication No. US 2020/0055900, the full disclosures of which are incorporated herein by reference in their entireties by reference for all purposes.

Intein-N and intein-C may be fused to the N-terminal portion of a split Cas9 and the C-terminal portion of the split Cas9, respectively, for the joining of the N-terminal portion of the split Cas9 and the C-terminal portion of the split Cas9. For example, in some embodiments, an intein-N is fused to the C-terminus of the N-terminal portion of the split Cas9, *i.e.*, to form a structure of N--[N-terminal portion of the split Cas9]-[intein-N]--C. In some embodiments, an intein-C is fused to the N-terminus of the C-terminal portion of the split Cas9, *i.e.*, to form a structure of N-[intein-C]--[C-terminal portion of the split Cas9]-C. In embodiments, a base editor is encoded by two polynucleotides, where one polynucleotide encodes a fragment of the base editor fused to an intein-N and another polynucleotide

encodes a fragment of the base editor fused to an intein-C. Methods for designing and using inteins are known in the art and described, for example by WO2014004336, WO2017132580, WO2013045632A1, US20150344549, and US20180127780, each of which is incorporated herein by reference in their entirety.

5 In some embodiments, an ABE was split into N- and C- terminal fragments at Ala, Ser, Thr, or Cys residues within selected regions of SpCas9. These regions correspond to loop regions identified by Cas9 crystal structure analysis.

The N-terminal fragment is fused at the C-terminus to an intein-N and the C-terminal fragment is fused to an intein-C at an N-terminal amino acid selected from the group
10 consisting of S303, T310, T313, S355, A456, S460, A463, T466, S469, T472, T474, C574, S577, A589, and S590, referenced to SEQ ID NO: 197. In various embodiments, the SpCas9 is split between amino acid positions 302 and 303, 309 and 310, 312 and 313, 354 and 355, 455 and 456, 459 and 460, 462 and 463, 465 and 466, 468 and 469, 471 and 472, 473 and 474, 573 and 574, 576 and 577, 588 and 589, or 589 and 590, referenced to SEQ ID NO: 197
15 to yield an N-terminal fragment and a C-terminal fragment, where the N-terminal fragment is fused at the C-terminus to an intein-N and where the C-terminal fragment is fused at the N-terminus to an intein-C.

PHARMACEUTICAL COMPOSITIONS

20 In some aspects, the present disclosure provides a pharmaceutical composition comprising any of the cells, polynucleotides, vectors, base editors, base editor systems, guide polynucleotides, fusion proteins, complexes, or the fusion protein-guide polynucleotide complexes described herein.

The pharmaceutical compositions of the present disclosure can be prepared in
25 accordance with known techniques. See, *e.g.*, Remington, The Science And Practice of Pharmacy (21st ed. 2005). In general, the cell, or population thereof is admixed with a suitable carrier prior to administration or storage, and in some embodiments, the pharmaceutical composition further comprises a pharmaceutically acceptable carrier. Suitable pharmaceutically acceptable carriers generally comprise inert substances that aid in
30 administering the pharmaceutical composition to a subject, aid in processing the pharmaceutical compositions into deliverable preparations, or aid in storing the pharmaceutical composition prior to administration. Pharmaceutically acceptable carriers can include agents that can stabilize, optimize or otherwise alter the form, consistency, viscosity, pH, pharmacokinetics, solubility of the formulation. Such agents include buffering agents,

wetting agents, emulsifying agents, diluents, encapsulating agents, and skin penetration enhancers. For example, carriers can include, but are not limited to, saline, buffered saline, dextrose, arginine, sucrose, water, glycerol, ethanol, sorbitol, dextran, sodium carboxymethyl cellulose, and combinations thereof.

5 In some embodiments, the pharmaceutical composition is formulated for delivery to a subject. Suitable routes of administering the pharmaceutical composition described herein include, without limitation: intravitreal, subretinal, suprachoroidal, topical, subcutaneous, transdermal, intradermal, intralesional, intraarticular, intraperitoneal, intravesical, transmucosal, gingival, intradental, intracochlear, transtympanic, intraorgan, epidural,
10 intrathecal, intramuscular, intravenous, intravascular, intraosseous, periocular, intratumoral, intracerebral, and intracerebroventricular administration.

In some embodiments, the pharmaceutical composition described herein is administered locally to a diseased site or source of a disease (*e.g.*, an organ, such as a liver). In some embodiments, the pharmaceutical composition described herein is administered to a
15 subject by injection, by means of a catheter, by means of a suppository, or by means of an implant, the implant being of a porous, non-porous, or gelatinous material, including a membrane, such as a sialastic membrane, or a fiber.

In some embodiments, any of the fusion proteins, gRNAs, and/or complexes described herein are provided as part of a pharmaceutical composition. In some
20 embodiments, the pharmaceutical composition comprises any of the fusion proteins or complexes provided herein. In some embodiments pharmaceutical composition comprises a gRNA, a nucleic acid programmable DNA binding protein, a cationic lipid, and a pharmaceutically acceptable excipient. In embodiments, pharmaceutical compositions comprise a lipid nanoparticle and a pharmaceutically acceptable excipient. In embodiments,
25 the lipid nanoparticle contains a gRNA, a base editor, a complex, a base editor system, or a component thereof of the present disclosure, and/or one or more polynucleotides encoding the same. Pharmaceutical compositions can optionally comprise one or more additional therapeutically active substances.

The compositions, as described above, can be administered in effective amounts. The
30 effective amount will depend upon the mode of administration, the particular condition being treated, and the desired outcome. It may also depend upon the stage of the condition, the age and physical condition of the subject, the nature of concurrent therapy, if any, and like factors well-known to the medical practitioner. For therapeutic applications, it is that amount sufficient to achieve a medically desirable result.

In some embodiments, compositions in accordance with the present disclosure can be used for treatment of any of a variety of diseases, disorders, and/or conditions.

METHODS OF TREATMENT

5 Some aspects of the present disclosure provide methods of treating a subject in need, the method comprising administering to a subject in need an effective therapeutic amount of a pharmaceutical composition as described herein. More specifically, the methods of treatment include administering to a subject in need thereof one or more pharmaceutical compositions comprising one or more cells having at least one edited gene. In other embodiments, the
10 methods of the disclosure comprise expressing or introducing into a cell a base editor polypeptide and one or more guide RNAs capable of targeting a nucleic acid molecule encoding at least one polypeptide.

 One of ordinary skill in the art would recognize that multiple administrations of the pharmaceutical compositions contemplated in particular embodiments may be required to
15 affect the desired therapy. For example, a composition may be administered to the subject 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more times over a span of 1 week, 2 weeks, 3 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 1 year, 2 years, 5, years, 10 years, or more.

 Administration of the pharmaceutical compositions contemplated herein may be carried out using conventional techniques including, but not limited to, infusion, transfusion,
20 or parenterally. In some embodiments, parenteral administration includes infusing or injecting intravascularly, intravenously, intramuscularly, intraarterially, intrathecally, intratumorally, intradermally, intraperitoneally, transtracheally, subcutaneously, subcuticularly, intraarticularly, subcapsularly, subarachnoidly and intrasternally.

Combination Therapy

 In various embodiments, methods of the present disclosure involve administering an inhibitor of a component of the complement system (e.g., of component C3 or factor B). In
embodiments, a pharmaceutical composition of the disclosure contains an inhibitor of
complement component C3. In embodiments, a pharmaceutical composition of the disclosure
30 contains an inhibitor of factor B. In some embodiments, the complement inhibitor is compstatin or a compstatin analog or mimetic.

 Drugs that inhibit complement system function are available and may be used in methods of the present disclosure. In embodiments, the drug is a small molecule, a nucleic acid molecule, a peptide, or an antibody. Non-limiting examples of such drugs include, but

are not limited to, EMPAVELI (Pegcetacoplan; APL-2), which targets C3, Danicopan (ACH-4471), which targets Factor D, Iptacopan (LPN 023), which targets factor B, siRNAs (Arrowhead ARO-C3), which targets C3, Amy 101, which targets C3, Eculizumab, which targets C5, Ravulizumab, which targets C5, Cemdisiran, which targets C5, OMS-721, which targets MASP2, IFX-1, which targets C5a, and Avacopan, which targets C5aR1.

Compstatin is a cyclic peptide that binds to C3 and inhibits complement activation.

U.S. Pat. No. 6,319,897 describes a peptide having the sequence I[CVVQDWGHHRC]T (SEQ ID NO: 3105), with the disulfide bond between the two cysteines denoted by brackets.

Morikis, et al., *Protein Sci.*, 7(3):619-27, 1998) also describe a compstatin. In some

instances, compstatin is amidated at the C-terminus. Compstatin analogs, mimetics, derivatives thereof, and/or compositions containing the same suitable for use in the methods and compositions of the present disclosure include those described in WO2021007111 (PCT/US2020/040741); WO2021011927 (PCT/US2020/042676); WO2004026328 (PCT/US2003/029653); Morikis, D., et al., *Biochem Soc Trans.* 32(Pt 1):28-32, 2004, Mallik, B., et al., *J. Med. Chem.*, 274-286, 2005; Katragadda, M., et al. *J. Med. Chem.*, 49: 4616-4622, 2006; WO2007062249 (PCT/US2006/045539); WO2007044668 (PCT/US2006/039397); WO2009046198 (PCT/US2008/078593); WO2010127336 (PCT/US2010/033345); WO2012155107; WO 2014078731; WO2019166411; WO2009121065; WO2021163654; WO2021142171; WO2017062879; WO2014152391; WO2014028861; WO2018187813; WO2019089653; WO2016049385; WO2018075373; WO2019118938; WO2022061304; WO2012006599; WO2011163394; WO2012178083; US9291622; US10407466; US8580735; and Hillmen, *et al.* "Pegcetacoplan versus Eculizumab in Paroxysmal Nocturnal Hemoglobinuria," *N Engl J Med.* 2021 Mar 18;384(11):1028-1037; the disclosures of all of which are incorporated herein by reference in their entireties for all purposes. In certain embodiments, a compstatin analog is pegcetacoplan ("APL-2"). Pegcetacoplan is also referred to as Poly(oxy-1,2-ethanediyl), α -hydro- ω -hydroxy-, 15,15'-diester with *N*-acetyl-L-isoleucyl-L-cysteiny-L-valyl-1-methyl-L-tryptophyl-L-glutaminy-L- α -aspartyl-L-tryptophylglycyl-L-alanyl-L-histidyl-L-arginyl-L-cysteiny-L-threonyl-2-[2-(2-aminoethoxy)ethoxy]acetyl-*N*⁶-carboxy-L-lysine cyclic (2->12)-(disulfide); or *O,O'*-bis[(*S*²,*S*¹²-cyclo{*N*-acetyl-L-isoleucyl-L-cysteiny-L-valyl-1-methyl-L-tryptophyl-L-glutaminy-L- α -aspartyl-L-tryptophylglycyl-L-alanyl-L-histidyl-L-arginyl-L-cysteiny-L-threonyl-2-[2-(2-aminoethoxy)ethoxy]acetyl-L-lysineamide})-*N*^{6,15}-carbonyl]polyethylene glycol (n = 800-1100).

In some embodiments, a complement inhibitor is an antibody, e.g., an anti-C3 antibody, or a fragment thereof. In some embodiments, an antibody fragment may be used to inhibit C3 activation. The antibody fragment may be Fab', Fab'(2), Fv, or a single chain Fv. In some embodiments, the anti-C3 antibody is monoclonal. In some embodiments, the anti-
5 antibody is polyclonal. In some embodiments, the anti-C3 antibody is de-immunized. In some embodiments the anti-C3 antibody is a fully human monoclonal antibody.

In some instances, a complement inhibitor is an inhibitory polynucleotide (e.g., an siRNA), such as those described in WO2021163654, the disclosure of which is incorporated herein in its entirety for all purposes.

10 In some embodiments, a complement inhibitor is a polypeptide inhibitor and/or a nucleic acid aptamer (see, e.g., U.S. Publ. No. 20030191084). Exemplary polypeptide inhibitors include an enzyme that degrades C3 or C3b (see, e.g., U.S. Pat. No. 6,676,943).

KITS

15 The invention provides kits for use in treating a subject to reduce complement activation. In some embodiments, the kit further includes a base editor system or a polynucleotide encoding a base editor system, wherein the base editor polypeptide system a nucleic acid programmable DNA binding protein (napDNAbp), a deaminase, and a guide RNA. In some embodiments, the napDNAbp is Cas9 or Cas12. In some embodiments, the
20 polynucleotide encoding the base editor is a mRNA sequence. In some embodiments, the deaminase is a cytidine deaminase or an adenosine deaminase. In some embodiments, the kit comprises a guide RNA and/or base editor system and instructions regarding the use of the guide RNA and/or base editor system.

The kits may further comprise written instructions for using a base editor, base editor
25 system and/or edited cell as described herein. In other embodiments, the instructions include at least one of the following: precautions; warnings; clinical studies; and/or references. The instructions may be printed directly on the container (when present), or as a label applied to the container, or as a separate sheet, pamphlet, card, or folder supplied in or with the container. In a further embodiment, a kit comprises instructions in the form of a label or
30 separate insert (package insert) for suitable operational parameters. In yet another embodiment, the kit comprises one or more containers with appropriate positive and negative controls or control samples, to be used as standard(s) for detection, calibration, or normalization. The kit can further comprise a second container comprising a pharmaceutically-acceptable buffer, such as (sterile) phosphate-buffered saline, Ringer's

solution, or dextrose solution. It can further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, syringes, and package inserts with instructions for use.

5 The practice of embodiments of the present disclosure employs, unless otherwise indicated, conventional techniques of molecular biology (including recombinant techniques), microbiology, cell biology, biochemistry and immunology, which are well within the purview of the skilled artisan. Such techniques are explained fully in the literature, such as, “Molecular Cloning: A Laboratory Manual”, second edition (Sambrook, 1989);
 10 “Oligonucleotide Synthesis” (Gait, 1984); “Animal Cell Culture” (Freshney, 1987); “Methods in Enzymology” “Handbook of Experimental Immunology” (Weir, 1996); “Gene Transfer Vectors for Mammalian Cells” (Miller and Calos, 1987); “Current Protocols in Molecular Biology” (Ausubel, 1987); “PCR: The Polymerase Chain Reaction”, (Mullis, 1994); “Current Protocols in Immunology” (Coligan, 1991). These techniques are applicable
 15 to the production of the polynucleotides and polypeptides of the disclosure, and, as such, may be considered in making and practicing embodiments of the disclosure. Particularly useful techniques for particular embodiments will be discussed in the sections that follow.

 The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the assay, screening, and
 20 therapeutic methods of the disclosure, and are not intended to limit the scope of what the inventors regard as their invention.

EXAMPLES

Example 1: Base editing of a complement factor B (CFB) polynucleotide to disrupt a splice site

25 Experiments were undertaken to develop base editor systems for altering a splice site of a CFB polynucleotide to reduce levels of functional CFB polypeptides in a cell or subject. The base editor systems were evaluated both *in vitro* and *in vivo*. It can be advantageous to silence or knock-out CFB in a subject as part of a treatment for a disease or disorder associated with inappropriate activation of the complement system.

30 Base editor systems were developed for disrupting a splice site of a CFB polynucleotide or introduce a stop codon and evaluated using HEK293T cells. The base editor systems contained a cytidine deaminase base editor (CBE) or an adenosine deaminase base editor (ABE) (e.g., ABE_NGC_20nt_3-9_008, ABE_NGG_20nt_3-9_002, ABE_NGA_20nt_3-9_005, ABE_NNGRRT_21nt_5-14_011, ABE_NNNRRT_21nt_5-

14_014, CBE_NNGRRT_21nt_3-12_012, CBE_NNNRRT_21nt_3-12_015, CBE_NGG_20nt_4-9_003, or CBE_NGA_20nt_4-9_006, where, throughout the Examples, the terms “NGC,” “NGG,” “NGA,” “NNGRRT,” and “NNNRRT” indicate the PAM specificity of the napDNAbp of each base editor, “ABE” indicates an adenosine deaminase base editor, “CBE” indicates a cytidine deaminase base editor, and “20nt” or “21nt” indicates the length of the spacer of the guide polynucleotide used in combination with the base editor) and a guide polynucleotides targeting a splice site of a CFB polynucleotide for base editing. Some of the base editor systems containing a CBE included a guide polynucleotide targeting the base editor to introduce a nucleotide modification to the CFB polynucleotide that resulted in the introduction of a new stop codon. The HEK293T cells were administered 800 ng total of the guide polynucleotide (200 ng) and mRNA encoding the base editor (600 ng). Seventeen (17) of the base editor systems containing an adenosine deaminase base editor and a guide polynucleotide were associated with maximum percents A to G base editing of greater than 50% (**FIG. 2; Table 8**). Twenty-seven (27) of the base editor systems containing a cytidine deaminase base editor and a guide polynucleotide were associated with maximum percents C to T base editing of greater than 50% (**FIG. 3**). The following guide polynucleotides were associated with maximum percents A to G base editing of greater than 50%: gRNA1210, gRNA1213, gRNA1181, gRNA1190, gRNA1185, gRNA1192, gRNA1202, gRNA1203, gRNA1218, gRNA1204, gRNA1217, gRNA1182, gRNA1230, gRNA1183, gRNA1187, gRNA1220, gRNA1193, gRNA1221, gRNA1204, gRNA1246, gRNA1408, gRNA1217, gRNA1361, gRNA1414, gRNA1409, gRNA1372, gRNA1413, gRNA1400, gRNA1370, gRNA1374, gRNA1412, gRNA1397, gRNA1373, gRNA1381, gRNA1394, gRNA1376, gRNA1389, gRNA1382, gRNA1396, gRNA1371, gRNA1378, gRNA1380, gRNA1379, and gRNA1384.

Table 8. Base editing rates associated with guides associated with maximum percents A to G base editing of greater than 50%.⁸

Guides*	Average	SD	Target Site	Cyno X Reactivity	Location
gRNA1193	86.43	1.1	TSBTx3826	Y	Exon 10-5'

⁸ The term “Cyno X Reactivity” refers to whether a guide targets both a human CFB and a cyno CFB for base editing (i.e., identified as “Y” and is cross-reactive) or whether a guide only targets a human CFB for base editing (i.e., identified as “N” and is not cross reactive). For each location listed in Table 8, the term “5” or “3” indicates the end of the exon closest to the splice site targeted for base editing. The term “SD” means standard deviation and the term “Average” indicates average maximum base editing measured in HEK293T cells.

Guides*	Average	SD	Target Site	Cyno X Reactivity	Location
sg23 (HPLC Exp1)	86.27	0.92			
sg23 (STANDARD)	84.55	1.43			
sg23 (HPLC)	84.03	3.39			
gRNA1220	83.01	2.41	TSBTx3853	N	Exon 10-3'
gRNA1187	74.4	0.87	TSBTx3820	N	Exon 1-3'
gRNA1183	74.18	0.68	TSBTx3816	N	Exon 18-5'
gRNA1230	72.38	0.93	TSBTx3863	Y	Exon 8-5'
gRNA1182	71.61	1.36	TSBTx3815	Y	Exon 14-5'
gRNA1217	71.06	0.67	TSBTx3850	Y	Exon 15-3'
gRNA1204	70.7	4.01	TSBTx3837	N	Exon 11-3'
gRNA1218	68.93	0.85	TSBTx3851	N	Exon 12-3'
gRNA1203	67.87	3.65	TSBTx3836	N	Exon 14-3'
gRNA1202	67.37	4.61	TSBTx3835	Y	Exon 16-3'
gRNA1192	65.96	8.8	TSBTx3825	Y	Exon 10-5'
gRNA1185	63.26	0.9	TSBTx3818	N	Exon 11-3'
gRNA1190	58.23	0.51	TSBTx3823	Y	Exon 9-5'
gRNA1181	56.32	0.7	TSBTx3814	Y	Exon 9-5'
gRNA1213	55.35	0.94	TSBTx3846	Y	Exon 11-5'
gRNA1210	53.52	1.84	TSBTx3843	Y	Exon 5-5'

*The terms “HPLC” and “STANDARD” refer to the methods by which the guides were purified. The sg23 guides were synthesized by Agilent and subsequently purified by Agilent using “HPLC” or “STANDARD” purification methods.

- 5 Having identified base editor systems associated with high base editing rates and containing one of the guides listed in **Table 8**, experiments were next undertaken to optimize the adenosine deaminase base editor used in the base editor systems. Maximum percent A to G base editing of a CFB polynucleotide was measured in HEK293T cells transfected with a guide polynucleotide and one of the adenosine deaminase base editors ABE8.8 Pre, ABE8.8,
- 10 ABE8.13, ABE8.17, ABE8.20, and ABE8.20 with the adenosine deaminase amino acid alteration V82T (ABE8.20+V82T) (see **FIG. 4**). The adenosine deaminase base editors each contained a Cas9 nickase domain that was capable of binding an NGG, NGA, or NNNRRT PAM sequence (see **FIG. 4**). A few of the base editor systems showed improved base editing rates when the adenosine deaminase base editor was changed to ABE8.13 or ABE8.17. The
- 15 following base editor systems showed good base editing rates, where, for each base editor system, the first term represents the guide polynucleotide, the letters following “ABE-” indicate the PAM specificity of the adenosine deaminase base editor, and the last numbers

indicate the identity of the adenosine deaminase domain of the base editor, where 8.8 refers to TadA*8.8, 8.13 refers to TadA*8.13, and 8.17 refers to TadA*8.17: gRNA1193:ABE-NGG_8.8; gRNA1220:ABE-NGA_8.8; gRNA1230:ABE-NNNRRT_8.8; gRNA1217:ABE-NGA_8.13; gRNA1204:ABE-NGG_8.8; gRNA1218:ABE-NGA_8.17; gRNA1203:ABE-NGG_8.13; gRNA1202:ABE-NGG_8.13; gRNA1190:ABE-NGG_8.8; gRNA1213:ABE-NGA_8.13; and gRNA1210:ABE-NGA_8.13.

Optimized base editor systems showing good maximum percent A to G base editing of a CFB polynucleotide in HEK293T cells were further evaluated in primary human hepatocyte(PHH) co-cultures. PHH transfected with polynucleotides encoding the base editor systems (i.e., a guide polynucleotide and mRNA encoding the base editor) showed high maximum A to G base editing at day 13 post-transfection and reduced levels of human CFB (hCFB) at day 11 post-transfection (**FIG. 5**).

To further optimize the base editor systems, an experiment was undertaken to optimize the length of the spacers of the guide polynucleotides (**FIG. 6**) used in three of the base editor systems. Percent CFB polynucleotide A to G base editing was measured in HEK293T cells transfected with mRNA encoding an adenosine deaminase base editor with specificity for an NGG PAM and with a gRNA1193 (TSBTx3826), gRNA1202 (TSBTx3835), or gRNA1204 (TSBTx3837) guide polynucleotide containing a spacer with a length of 19 nt, 20 nt, 21 nt, 22 nt, or 23 nt (**FIG 6**). The cells were transfected using 100 ng of the guide polynucleotide and 300 ng mRNA encoding the adenosine deaminase base editor. The highest percents CFB polynucleotide A to G base editing were associated with spacers that were 20 nt or 21 nt in length (**FIG. 6**).

Optimal spacer length was further evaluated using human hepatocytes isolated from a PXB-mouse (PXB cells) (**FIG. 7B**). Percent CFB polynucleotide A to G base editing and human CFB (hCFB) protein levels were measured in PXB cells transfected with mRNA encoding an adenosine deaminase base editor (ABE8.8 or ABE8.13) with specificity for an NGG PAM and with a TSBTx3826 (e.g., gRNA1193), TSBTx3835 (e.g., gRNA1202), or TSBTx3837 (e.g., gRNA2067) guide polynucleotide containing a spacer with a length of 19 nt, 20 nt, 21 nt, 22 nt, or 23 nt (**FIG 7A**). The cells were transfected using 150 ng of the guide polynucleotide and 450 ng mRNA encoding the adenosine deaminase base editor. The base editor systems were associated with high maximum percents A to G base editing and reductions in hCFB protein levels.

Editing efficiency for base editor systems containing guide polynucleotides cross-reactive (i.e., capable of targeting both a non-human primate and a human CFB polynucleotide for base editing) and cyno-surrogate (i.e., capable of targeting a non-human primate CFB polynucleotide for base editing) guide polynucleotides was evaluated using primary cyno hepatocyte (PCH) co-cultures (**FIGs. 8A and 8B**). The CFB co-cultures were transfected with mRNA encoding an adenosine deaminase base editor (ABE8.8 or ABE8.13) and the guide polynucleotide gRNA1193, gRNA2072, or gRNA1202. The base editor systems were associated with maximum percents CFB A to G editing of greater than about 60% (**FIG. 8A**) and with reductions in cyno CFB protein levels in the PCH (**FIG. 8B**).

Table 9 provides a description of the ABE-encoding mRNA molecules used in the examples and the ABEs encoded by the same.

Table 9. Description of mRNA molecules encoding base editors used in the Examples. Throughout the disclosure, the term “MRNA” in each mRNA name may be replaced with the term “m.”

mRNA name	TadA*	Linker*	Cas9
MRNA3171	8.8	32aa (original)	WT
MRNA3534	8.8	32aa (original)	WT
MRNA3535	8.13	32aa (original)	WT
MRNA3536	8.17	32aa (original)	WT
MRNA3537	8.20	32aa (original)	WT
MRNA3538	8.8 +V82T	32aa (original)	WT
MRNA3539	8.8 +V82T+Y147T+Q154S	32aa (original)	WT
MRNA3540	8.17 +V82T	32aa (original)	WT
MRNA3541	8.17 +V82T+Y147T+Q154S	32aa (original)	WT
MRNA3542	8.20 +V82T	32aa (original)	WT
MRNA3543	8.20 +V82T+Y147T+Q154S	32aa (original)	WT
MRNA3544	8.13-m	32aa (original)	A1283D
MRNA3545	8.13-m	32aa (original)	A1283D + E1250K
MRNA3546	8.13-m	32aa (original)	Q844R, V842L, F846Y, L847M and I852F (TurboCas9)
MRNA3547	8.13-m	KGPKPKKEESEK (SEQ ID NO: 3106)	A1283D
MRNA3548	8.13-m	KGPKPKKEESEK (SEQ ID NO: 3106)	A1283D + E1250K

mRNA name	TadA*	Linker*	Cas9
MRNA3549	8.13-m	KGPKPKKEESEK (SEQ ID NO: 3106)	Q844R, V842L, F846Y, L847M and I852F (TurboCas9)

*The term “32aa (original)” refers to a linker with the following amino acid sequence:

SGGSSGGSSGSETPGTSESATPESSGGSSGGS (SEQ ID NO: 357).

The base editor systems were further optimized by evaluating maximum percent CFB A to G base editing in HepG2 cells (**FIGs. 9B-9D**), which are human liver cancer cell line derived from the liver tissue of a 15-year-old Caucasian male with a hepatocellular carcinoma, and in primary human hepatocytes (**FIG. 9A**) transfected with different doses of a gRNA2445 (TSBTx3826; NLS nucleotide modification scheme), gRNA2451 (TSBTx3837; HM01 nucleotide modification scheme), or gRNA1202 (TSBTx3835; End-Mod nucleotide modification scheme) guide polynucleotide and a constant dose of one of the mRNA's of **Table 9** encoding an adenosine deaminase base editor (**FIGs. 9A-9D**). The following base editor systems showed high maximum percents CFB A to G base editing, where the term following the underscores (“_”) and before the plus signs (“+”) indicate the guide polynucleotide nucleotide modification scheme: gRNA2445(TSBTx3826)_NLS+ABE8.8; gRNA2445(TSBTx3826)_NLS+ABE8.20; gRNA2445(TSBTx3826)_NLS+ an ABE8.20 with a TadA*8.20 adenosine deaminase domain containing the alterations V82T, Y147T, and Q154S; gRNA2451(TSBTx3837)_HM01+ABE8.8; gRNA2451(TSBTx3837)_HM01+ABE8.20; gRNA1202(TSBTx3835)_End-Mod+ABE8.13; gRNA1202(TSBTx3835)_End-Mod+ an ABE8.20 with a TadA*8.20 adenosine deaminase domain containing the alterations V82T, Y147T, and Q154S.

Experiments were next undertaken to evaluate the ability of the optimized base editor systems to mediate base editing of a complement factor B (CFB) polynucleotide in FRGTM liver-humanized mice. The FRGTM humanized mice were administered lipid nanoparticles containing mRNA encoding the adenosine deaminase base editor ABE8.8 and either 2 mg/kg (mpk) or 0.3 mpk of a gRNA1193 (TSBTx3826; end-mod nucleotide modification scheme) guide polynucleotide. Maximum percents A to G editing and percent indel formation (**FIG. 10A**) and human CFB (hCFB) levels (**FIG. 10B**) were measured in the mice prior to administration (i.e., day 0 pre-dose), at day 7 post-administration, and at day 14 post-administration (experiment termination). For a dose of 2.0 mpk of gRNA1193, a percent

maximum A to G editing of about 53% was measured together with a reduction in CFB protein levels of about 45%. For a dose of 0.3 mpk of gRNA1193, a percent maximum A to G editing of about 18% was measured together with a reduction in CFB protein levels of about 20%. The base editor systems were associated with minimal indel formation. A time-
5 dependent decrease in hCFB polypeptide levels was observed (**FIG. 10B**). Interestingly, it was observed that as factor B protein levels decreased in the mice, C3 protein levels increased but C3 mRNA levels remained unchanged at day 14 in the FRGTM humanized mice (**FIG. 11**). Without intending to be bound by theory, removing factor B may result in lower C3 convertase and, thus, slowed breakdown/consumption of C3 and an apparent increase in
10 amount of protein level without impacting mRNA levels. Also, as C3 protein levels decreased, factor B mRNA and protein levels increased at day 14 in the FRGTM humanized mice (**FIG. 11**).

To assist in further optimizing the base editor systems, experiments were undertaken to determine the impact of guide polynucleotide nucleotide modification schemes and base
15 editor selection on base editing in FRGTM liver-humanized mice (**FIGs. 12A, 12B, 13, 14A, 14B, 15, 16A, 16B, and 17**). FRGTM liver-humanized mice were administered lipid nanoparticles containing a base editor system containing a TSBTx3826 (**FIGs. 12A, 12B, and 13**), TSBTx3837 (**FIGs. 14A, 14B, and 15**), or TSBTx3835 (**FIGs. 16A, 16B, and 17**) guide polynucleotide with a nucleotide modification scheme selected from End-Mod, HM01,
20 HM07, NLS, and Longest, and an mRNA encoding an adenosine base editor selected from ABE8.8, ABE8.20, and ABE8.20 with a TadA*8.20 adenosine deaminase domain containing the alterations V82T, Y147T, and Q154S. The mice were administered either 0.5 mpk or 0.3 mpk of the guide polynucleotides. Following administration of the base editor systems, percents CFB A to G editing, human CFB (hCFB) polypeptide levels, and hCFB mRNA
25 levels were measured at 14-days post-administration. The following base editor systems were associated with high percents A to G editing and reduced hCFB protein levels in tissues of the mice: TSBTx3826 guide polynucleotide with an NLS nucleotide modification scheme + ABE8.20 with a TadA*8.20 adenosine deaminase domain containing the alterations V82T, Y147T, and Q154S; TSBTx3837 guide polynucleotide with an HM01 nucleotide
30 modification scheme + ABE8.20; TSBTx3835 guide polynucleotide with an HM01 nucleotide modification scheme + ABE8.20 with a TadA*8.20 adenosine deaminase domain containing the alterations V82T, Y147T, and Q154S. Tissue hCFB mRNA levels measured in mice administered a base editor system containing a TSBTx3826 guide polynucleotide were consistent with disruption of mRNA splicing.

Experiments were undertaken to compare the potency (i.e., maximum percent A to G editing at a set dose of guide polynucleotide) in primary human hepatocytes (PHH) and primary cyno hepatocytes (PCH) of base editor systems containing varying doses of the guide nucleotide TSBTx3837, TSBTx4943, or TSBTx3826 (see **FIG. 18** and **Table 10**). The PHH and PCH cells were transduced with the indicated guide polynucleotide and mRNA encoding an adenosine deaminase base editor (ABE8.8) at a mass ratio of 1-to-3 (1:3). The base editor systems were more potent in PHH than in PCH.

Table 10. Comparison of base editor system potency in primary human hepatocytes (PHH) and primary cyno hepatocytes (PCH).⁹

Target Site	Guide	EC-50	R-square	EC-50 fold change	
TSBTx3837	gRNA2067	3.351	0.9967	~2.83x	PHH
	gRNA2072	9.477	0.9973		PCH
TSBTx3826	gRNA1193	4.286	0.9956	~3.75x	PHH
	gRNA1193	16.07	0.9984		PCH
ALAS1	sg23	0.2563	0.9929	~4.53x	PHH
	sg23	1.161	0.9722		PCH

Experiments were undertaken to compare the potency (i.e., maximum percent A to G editing at a set dose of guide polynucleotide) in HEK293T cells containing the polynucleotide construct of **FIG. 19A** of a base editor systems containing the guide nucleotide TSBTx3837 (see **FIGs. 19B-19D** and **Table 11**). The HEK293T cells, which contained the polynucleotide construct of **FIG. 19A** within their genomes, were transduced with varying doses the TSBTx3837 guide polynucleotide and mRNA encoding an adenosine deaminase base editor (ABE8.8).

⁹ EC-50 was calculated based on guide polynucleotide (gRNA) dose. R-square indicates the R-square value for the curve fit to the data to calculate the EC-50 values.

Table 11. Potency comparison of a base editor system containing a TSBTx3837 guide polynucleotide in HEK293T cells for editing a human or non-human primate complement factor B polynucleotide.

CFB (TSBTx3837)	Guide	Batch 1		Batch 2		Batch 3	
		EC50	R-square	EC50	R-square	EC50	R-square
Human	gRNA2067 (TSBTx3837)	1.252	0.9121	0.8465	0.8331	1.982	0.8008
NHP	gRNA2072 (TSBTx4943)	0.5124	0.9242	0.4249	0.817	4.162	0.947

Table 12 provides a summary of data gathered through the above-describe experiments relating to base editor systems containing one of three representative guide polynucleotides.

Table 12. Data relating to representative base editor systems.

Guide polynucleotide	TSBTx3826	TSBTx3837	TSBTx3835
Mod-Scheme	NLS	HM01	HM01
PAM sequence	NGG	NGG	NGG
Spacer length (nt)	20	21	20
Base Editor	8.20 +V82T+Y147T+Q154S	ABE8.20	8.20 +V82T+Y147T+Q154S
Cross-reactive with a non-human primate CFB polynucleotide?	Yes	No - 1nt difference (no potency difference when using NHP surrogate guide)	Yes
Location (5' or 3' indicates the position of the target site relative to the indicated Exon)	Exon 10-5'	Exon 11-3'	Exon 16-3'
Base Editing Percent (0.3 mpk dose of guide polynucleotide)	32.82% (sg23@38.8%)	37.32% (sg23@68.92%)	36.42% (sg23@68.92%)
Protein Level Reduction Post-Editing Relative to Predose (0.3 mpk dose of guide polynucleotide)	48.2% (sg23 target polynucleotide-encoded polypeptide @80% pre-dose level)	54.5% (sg23 target polynucleotide-encoded polypeptide @102% pre-dose level)	56.8% (sg23 target polynucleotide-encoded polypeptide @102% pre-dose level)
Ratio of terminal CFB mRNA levels to sg23 target polynucleotide mRNA levels post-editing (0.3 mpk dose of guide polynucleotide)	38.40%	64.30%	113%
Off-Target (OT) editing (see Example 4)	<u>NLS & ABE8.8</u> very low editing frequency of OT gene HCK, Src family of tyrosine kinases	<u>HM01 & ABE8.8</u> No OT editing risk identified	<u>End-Mod & ABE8.13</u> No OT editing risk identified

Example 2: Base editing of a complement factor B (CFB) polynucleotide to disrupt a TATA box or alter a translation start codon (AUG)

Experiments were undertaken to develop base editor systems for altering a start codon or TATA box of a CFB polynucleotide to reduce levels of functional CFB polypeptides in a cell. TATA Box, also called the Goldberg–Hogness box is a DNA sequence found in the core promoter region of a gene. It is considered a non-coding DNA sequence and important to regulating gene transcription. The base editor systems were evaluated *in vitro*.

Base editor systems were developed for altering a TATA box of a CFB polynucleotide and evaluated using HepG2 cells. A predicted TATA Box corresponding to positions -157 to -151 of the CFB gene relative to start Codon was targeted for editing. The base editor systems contained mRNA encoding an adenosine deaminase base editor (ABE_NGG_20nt_3-9_002 (abe8.8); NGA IBE16 ABE8.20 SpCas9; NGG IBE16 ABE8.20 SpCas9; NGC ABE_8.20_IBE16_SpCas9; ABE_NNNRRT_21nt_5-14_014; ABE_NGA_20nt_3-9_005; or ABE_8.20_SpCas9_NGC-002, where, throughout the Examples, the terms “NGG,” “NGA,” “NGC,” “NNNRRT,” and “NNGRRT” indicate the PAM binding specificity of the napDNAbp of each base editor, “IBE16” indicates a base editor with the adenosine deaminase domain inserted within the napDNAbp domain, “ABE8.8” indicates an ABE8.8 base editor, “21nt” or “20nt” indicates the length of the spacer of the guide polynucleotide used in combination with the base editor, “8.20” indicates a base editor containing a Tada*8.20 adenosine deaminase domain, and “SpCas9” indicates an SpCas9 napDNAbp domain) and a guide RNA targeting a TATA box of a CFB polynucleotide for base editing. Ten (10) of the base editor systems contained the same guide RNA but mRNA encoding a different base editor. The base editor systems corresponding to Sample 1 through Sample 16 of FIG. 20 are also listed in Table 12.1A.

Table 12.1A. Base editor systems used to alter a TATA box in HepG2 cells.

Samples	gRNA #	mRNA #	Base Editor Name	Template Plasmid
Sample 1	gRNA3654	mRNA2743	ABE8.20 NGC	pST-107
Sample 2	gRNA3656	MRNA1021	ABE 8.8 NNNRRT	pMSP985
Sample 3	gRNA3651	mRNA3171	ABE8.8 NGG	pMSP546
		mRNA3169	ABE8.20 IBE16 NGG	pCR-007
Sample 4	gRNA3652	mRNA1992	VRQR spCas9-ABE8.8 NGA	pMSP981
Sample 5	gRNA3655	MRNA1021	ABE 8.8 NNNRRT	pMSP985
Sample 6	gRNA3649	mRNA3169	ABE8.20 IBE16 NGG	pCR-007

Samples	gRNA #	mRNA #	Base Editor Name	Template Plasmid
		mRNA3171	ABE8.8 NGG	pMSP546
Sample 7	gRNA3648	mRNA3169	ABE8.20 IBE16 NGG	pCR-007
		mRNA3171	ABE8.8 NGG	pMSP546
Sample 8	gRNA3647	mRNA3171	ABE8.8 NGG	pMSP546
		mRNA3169	ABE8.20 IBE16 NGG	pCR-007
Sample 9	gRNA3642	mRNA3171	ABE8.8 NGG	pMSP546
		mRNA3169	ABE8.20 IBE16 NGG	pCR-007
Sample 10	gRNA3653	mRNA2743	ABE8.20 NGC	pST-107
Sample 11	gRNA3650	mRNA3171	ABE8.8 NGG	pMSP546
		mRNA3169	ABE8.20 IBE16 NGG	pCR-007
Sample 12	gRNA3643	mRNA3169	ABE8.20 IBE16 NGG	pCR-007
		mRNA3171	ABE8.8 NGG	pMSP546
Sample 13	gRNA3645	mRNA3171	ABE8.8 NGG	pMSP546
		mRNA3169	ABE8.20 IBE16 NGG	pCR-007
Sample 14	gRNA3644	mRNA3169	ABE8.20 IBE16 NGG	pCR-007
		mRNA3171	ABE8.8 NGG	pMSP546
Sample 15	gRNA3646	mRNA3171	ABE8.8 NGG	pMSP546
		mRNA3169	ABE8.20 IBE16 NGG	pCR-007
Sample 16	sgRNA 088	mRNA3171	ABE8.8 NGG	pMSP546

The HepG2 cells were plated on Day 1 of the experiment. Media was changed on the 2nd day followed by transfection with the base editor systems using LIPOFECTAMINE® MESSANGERMAX®. The HepG2 cells were administered 800 ng total of the guide polynucleotide (200 ng) and mRNA encoding the base editor (600 ng). Media was changed on Day 3 and the cells were taken down on Day 5. Quick Extract (QE) buffer was used for cell lysis and genomic DNA (gDNA) extraction. A library was generated and sequenced using next-generation sequencing (NGS) technology.

Twelve (12) of the base editor systems of **Table 12.1A** were associated with maximum percents A to G base editing of greater than 30% (**FIG. 20**). The CFB TATA box is located at positions -157 to -151 relative to the CFB polynucleotide start codon. The TATA box nucleotide positions relative to the CFB polynucleotide start codon targeted for base editing by the guide polynucleotides were as follows: gRNA3643: -156; -154; gRNA3644: -156, -154; gRNA3645: -156; -154; gRNA3646: -156; -154; gRNA3647: -154; -153; 152; gRNA3648: -154; -152; -151; gRNA3649: -154; -153; -152; -151; gRNA3650: -155; -157; gRNA3652: -154; -151; gRNA3655: -156; -154. The guide polynucleotides each targeted multiple TATA box sites for base editing. Out of 15 CFB TATA Box gRNAs assessed, 12 showed >30% editing and were further assessed for base editing in Primary Human Hepatocytes (PHH).

Base editor systems were developed for altering the start codon of a CFB polynucleotide and evaluated using HepG2 cells (**FIG. 21A**) and in a primary human hepatocyte (PHH) monolayer (**FIG. 21B**). The base editor systems contained a adenosine deaminase base editor (ABE_NGG_20nt_3-9_002 (abe8.8); NGA IBE16 ABE8.20 SpCas9; NGG IBE16 ABE8.20 SpCas9; NGC ABE_8.20_IBE16_SpCas9; ABE_NNNRRT_21nt_5-14_014; ABE_NGA_20nt_3-9_005; or ABE_8.20_SpCas9_NGC-002) and a guide polynucleotides targeting the start codon of a CFB polynucleotide for base editing. The base editor systems corresponding to Sample 1 through Sample 8 of **FIG. 21A** and Sample 1 through Sample 3 of **FIG. 21B** are also listed in **Table 12.1B**.

The HepG2 cells were plated on Day 1 of the experiment. Media was changed on the 2nd day followed by transfection with the base editor systems using LIPOFECTAMINE® MESSANGERMAX®. The cells were administered 800 ng total of the guide polynucleotide (200 ng) and mRNA encoding the base editor (600 ng). Media was changed on Day 3 and the cells were taken down on Day 5. Quick Extract (QE) buffer was used for cell lysis and genomic DNA (gDNA) extraction. A library was generated and sequenced using next-generation sequencing (NGS) technology. The guide polynucleotides gRNA3658 and gRNA3660 were both associated with percent A to G base editing rates of greater than 70% in the HepG2 cells (**FIG. 21A**).

Table 12.1B. Base editor systems used to alter a start codon box in HepG2 cells and PHH monoculture.

	Samples	gRNA #	mRNA#	Base Editor Name	Template Plasmid
CFB_KO Start Site Guides in HepG2	Sample 1	gRNA3661	mRNA1992	VRQR spCas9-ABE8.8 NGA	pMSP981
	Sample 2	gRNA3659	MRNA3169	ABE8.20 IBE16 NGG	pCR-007
	Sample 3	gRNA3662	mRNA3165	ABE8.20 IBE16 NGA	pCR-001
	Sample 4	gRNA3661	mRNA3165	ABE8.20 IBE16 NGA	pCR-001
	Sample 5	gRNA3660	mRNA3165	ABE8.20 IBE16 NGA	pCR-001
	Sample 6	gRNA3658	MRNA3169	ABE8.20 IBE16 NGG	pCR-007
	Sample 7	gRNA3660	mRNA1992	VRQR spCas9-ABE8.8 NGA	pMSP981
	Sample 8	sgRNA 088	mRNA3171	ABE8.8 NGG	pMSP546
CFB_KO Start Site gRNA3657 in PHH	Sample 1	gRNA3657	mRNA3167	ABE8.20 IBE16 NGC	pCR-004
	Sample 2	gRNA3657	mRNA2743	ABE8.20 NGC	pST-107
	Sample 3	sgRNA 088	mRNA3171	ABE8.8 NGG	pMSP546

The primary human hepatocyte (PHH) cells were seeded in the morning and transfected with the base editor systems 4 hours after seeding. The cells were transfected with the base editor systems of **Table 12.1B** using LIPOFECTAMINE® MESSANGERMAX®. Media was changed on the next day. The cells were taken down on Day 4 post-seeding.

5 Quick Extract (QE) buffer was used for cell lysis and genomic DNA (gDNA) extraction. A library was generated and sequenced using the NGS technology. The data was analyzed and graphed (**FIG. 21B**). The base editor system containing gRNA3657 and the base editor encoded by mRNA2743 yielded on-target editing and a low frequency of bystander edits in the PHH monolayer.

10 Base editor systems that performed well in the above-described experiments for editing the CFB polynucleotide TATA box or start codon were further evaluated using a primary human hepatocyte (PHH) co-culture system to assess base editing rates and the effect of base editing on secreted CFB protein levels in supernatant (**FIGs. 22A and 22B**). Maximum percents CFB polynucleotide A to G base editing and human CFB (hCFB) protein
15 levels were measured in PHH transfected with base editor systems containing mRNA encoding an adenosine deaminase base editor (ABE_NGG_20nt_3-9_002 (abe8.8); NGA IBE16 ABE8.20 SpCas9; NGG IBE16 ABE8.20 SpCas9; NGC ABE_8.20_IBE16_SpCas9; ABE_NNNRRT_21nt_5-14_014; ABE_NGA_20nt_3-9_005; or ABE_8.20_SpCas9_NGC-002) and a guide polynucleotide targeting the CFB polynucleotide TATA box or start codon
20 for base editing. The base editor systems corresponding to Sample 1 through Sample 16 of **FIG. 22A** are also listed in **Table 12.1C**. Sample 16 was a negative control that did not contain any base editor system components. The PHH were co-cultured with 3T3-J2 mouse feeder cells.

25 **Table 12.1C. Base editor systems used for function and editing validation in PHH co-culture.**

Samples	gRNA #	mRNA#	Base Editor Name	Template Plasmid
Sample 1	gRNA3649	mRNA3169	ABE8.20 IBE16 NGG	pCR-007
Sample 2	gRNA3648	mRNA3169	ABE8.20 IBE16 NGG	pCR-007
Sample 3	gRNA3655	mRNA1021	ABE 8.8 NNNRRT	pMSP985
Sample 4	gRNA3647	mRNA3171	ABE8.8 NGG	pMSP546
Sample 5	gRNA3642	mRNA3171	ABE8.8 NGG	pMSP546
Sample 6	gRNA3653	mRNA2743	ABE8.20 NGC	pST-107
Sample 7	gRNA3650	mRNA3171	ABE8.8 NGG	pMSP546
Sample 8	gRNA3643	mRNA3171	ABE8.8 NGG	pMSP546
Sample 9	gRNA3645	mRNA3171	ABE8.8 NGG	pMSP546

Samples	gRNA #	mRNA#	Base Editor Name	Template Plasmid
Sample 10	gRNA3652	mRNA1992	VRQR spCas9-ABE8.8 NGG	pMSP981
Sample 11	gRNA3646	mRNA3171	ABE8.8 NGG	pMSP546
Sample 12	gRNA3644	mRNA3171	ABE8.8 NGG	pMSP546
Sample 13	gRNA3658	mRNA3169	ABE8.20 IBE16 NGG	pCR-007
Sample 14	gRNA3660	mRNA1992	VRQR spCas9-ABE8.8 NGG	pMSP981
Sample 15	sgRNA 088	mRNA3171	ABE8.8 NGG	pMSP546
Sample 16	N/A	N/A	N/A	N/A

The PHH were seeded on Day -6 and the feeder cells were added on Day -5 to form the co-culture system. Media was changed on the next day. On Day -3 to Day 0 (72 hours) media was collected as a baseline sample for ELISA (enzyme-linked immunosorbent assay) and the PHH were transfected on Day 0. Transfection with phosphate buffered saline (PBS) was used as a negative control (Sample 16). A base editor system targeting ALAS1 (Sample 15) for editing was used as a positive editing control and negative protein reduction control. The cells were transfected with the base editor systems using LIPOFECTAMINE® MESSANGERMAX®. Media was changed on the next day and then every 2-3 days. Supernatant was collected from the last 72 hours of the culture for ELISA. The ELISA results (FIG. 22A) were normalized to the pre-transfection baseline. The following kit was used for the ELISA: ab137973 Human Factor B ELISA Kit. The PHH co-culture system was taken down on Day 12. The cells were in culture for a total of 18 days. Quick Extract (QE) buffer was used for cell lysis and genomic DNA (gDNA) extraction. A library was generated and sequenced using next-generation sequencing (NGS) technology.

A number of the base editor systems of **Table 12.1C** were associated with high maximum percents A to G base editing and reductions in hCFB protein levels. In particular, the guides gRNA3658 and gRNA3660, which targeted the CFB polynucleotide start codon for base editing, were associated with percents maximum A to G base editing at day 13 post-transfection of greater than around 30% and with reductions in hCFB protein levels at day 12 post-transfection (FIG. 22A).

Base editor systems targeting the CFB polynucleotide start codon for base editing and containing one of the guide polynucleotides gRNA3657, gRNA3658, and gRNA3660 were further evaluated in primary human hepatocyte (PHH) co-cultures (FIGs. 23 and 25). Percents CFB polynucleotide A to G base editing and human CFB (hCFB) protein levels were measured in PHH co-cultures transfected with base editor systems containing mRNA encoding an adenosine deaminase base editor (ABE_NGG_20nt_3-9_002 (abe8.8); NGG IBE16 ABE8.20 SpCas9; NGC ABE_8.20_IBE16_SpCas9; ABE_8.20_SpCas9_NGC-002;

pHRB-445_From_pHRB-438 E59A, N108D-001; pHRB-446_From_pHRB-439-001; pHRB-449_From_pHRB-442-001) with specificity for an NGC, NGG, or GNA PAM sequence, and a guide polynucleotide targeting the CFB polynucleotide start codon for base editing. The base editor systems corresponding to Sample 1 through Sample 9 of **FIG. 25** are also listed in

- 5 **Table 12.1D.** The base editor systems of Samples 4 to 6 contained mRNA encoding catalytically inactive base editor polypeptides (dead TadA) and were used as negative controls. A base editor system containing a gRNA1193 targeting a splice site for editing was used as a positive control. Sample 9 was a negative control that did not contain any base editor system components.

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Table 12.1D. Base editor systems used for function and editing validation in PHH co-culture. Catalytically inactive editors are shown in bold text.

Samples	gRNA #	mRNA#	Base Editor Name	Template Plasmid
Sample 1	gRNA3657	mRNA2743	ABE8.20 NGC	pST-107
Sample 2	gRNA3658	mRNA3169	ABE8.20 IBE16 NGG	pCR-007
Sample 3	gRNA3660	mRNA1992	VRQR spCas9- ABE8.8 NGA	pMSP981
Sample 4	gRNA3657	mRNA3410	dABE8.20 NGC	pHRB-449 From pHRB-442
Sample 5	gRNA3658	mRNA3406	dABE8.20 NGG	pHRB-445 From pHRB-438 E59A, N108D
Sample 6	gRNA3660	mRNA3407	dABE8.20 NGA	pHRB-446 From pHRB-439
Sample 7	gRNA1193	mRNA3171	ABE8.8 NGG	pMSP546
Sample 8	sgRNA 088	mRNA3171	ABE8.8 NGG	pMSP546
Sample 9	N/A	N/A	N/A	N/A

- The PHH co-cultures were prepared by co-culturing PHH with 3T3-J2 mouse feeder
- 15 cells. The PHH were seeded on Day -6 and the feeder cells were added on Day -5 to form a co-culture system. Media was changed on the next day. On Days -3 to 0 (72 hours), media was collected as a baseline sample for ELISA and the cells were transfected with the base editor systems on Day 0. The cells were transfected with the base editor systems using LIPOFECTAMINE® MESSANGERMAX®. Transfection with phosphate buffered saline
- 20 (PBS) was used as a negative control (Sample 9). The cells were administered 800 ng total of the guide polynucleotide (200 ng) and mRNA encoding the base editor (600 ng). Media was changed the day after transfection and then every 3 days. Supernatant was collected for ELISA evaluation on Days 7, 10, and 13 post-transfection. The ELISA results were normalized to pre-transfection baseline (**FIGs. 23 and 25**). The following kit was used for the
- 25 ELISA: ab137973 Human Factor B ELISA Kit.

The base editor systems of **Table 12.1D** were associated with reductions in hCFB polypeptide levels at days 12 and 13 post-transfection. The base editor systems were also associated with base editing rates of greater than about 60%. An experiment was undertaken to demonstrate sustained reductions in hCFB protein levels following base editing of an hCFB polynucleotide start codon in a long-term (~22 days) HepG2 culture system (**FIG. 26B**) using the base editor systems listed in **Table 12.1E** and corresponding to Samples 1 to 8 (**FIGs. 26A and 27**). Sample 8 of **Table 12.1E** was a phosphate buffered saline (PBS) negative control that did not contain any component of a base editor system, and Sample 7 was a positive control base editor system targeting ALAS1 for editing. The base editor systems contained mRNA encoding a base editor together with a gRNA molecule. The cells were plated on Day -1 and transfected with the base editor systems the next day using LIPOFECTAMINE® MESSANGERMAX®. Transfection with phosphate buffered saline (PBS) was used as a negative control (Sample 8). As negative controls, the cells were also transfected with base editor systems containing mRNA encoding a catalytically inactive base editor. Media was changed every two days after the transfection. Media was collected on days 10, 14, 18, and 22 post-transfection for evaluation using ELISA (enzyme-linked immunosorbent assay). Cells were taken down 22 days post-transfection. Quick Extract (QE) buffer was used for cell lysis and genomic DNA (gDNA) extraction. A library was generated and sequenced using next-generation sequencing (NGS) technology. The following kit was used for the ELISA: ab137973 Human Factor B ELISA Kit.

Table 12.1E. Base editor systems used for functional assessment of start codon targeting guides in a long-term HepG2 culture system. Catalytically inactive editors are shown in bold text. “ABE9.52” refers to a base editor containing the following adenosine deaminase domain: TadA*8.20 with the amino acid alterations V82T, Y147T, and Q154S.

Guide Group	Samples	gRNA #	mRNA#	BE Name	Template Plasmid
CFB_KO TATA Box	Sample 1	gRNA3649	mRNA3171	ABE8.8_NGG	pMSP546
			mRNA3406	dABE8.20_NGG	pHRB-445_From_pHRB-438 E59A, N108D
	Sample 2	gRNA3655	mRNA1021	ABE 8.8 NNNRRT	pMSP985
			mRNA3409	dABE8.20 NNNRRT	pHRB-448_From_pHRB-441
		gRNA3657	mRNA2743	ABE8.20_NGC	pST-107

CFB_KO Start Site	Sample 3		mRNA3410	dABE8.20_NGC	pHRB-449_From_pHRB-442
	Sample 4	gRNA3658	mRNA3169	ABE8.20_IBE16_NGG	pCR-007
			mRNA3406	dABE8.20_NGG	pHRB-445_From_pHRB-438 E59A, N108D
	Sample 5	gRNA3660	mRNA1992	VRQR spCas9-ABE8.8_NGA	pMSP981
			mRNA3407	dABE8.20_NGA	pHRB-446_From_pHRB-439
CFB_KO Splice Site	Sample 6	gRNA2445	mRNA3969	ABE9.52	pMSP1197
			mRNA3406	dABE8.20_NGG	pHRB-445_From_pHRB-438 E59A, N108D
ALAS1 Control	Sample 7	gRNA_088	mRNA3171	ABE8.8_NGG	pMSP546
			mRNA3406	dABE8.20_NGG	pHRB-445_From_pHRB-438 E59A, N108D
N/A	Sample 8	N/A	N/A	N/A	N/A

Many of the base editor systems of **Table 12.1E** were associated with greater than about 60% base editing rates (**FIG. 26A**), and all base editor systems targeting an hCFB start site for editing were associated with a lasting reduction in hCFB protein levels (**FIG. 27**)

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Example 3: Assessment of possible off-target base editing mediated by guide polynucleotides of the disclosure

Some base editors and/or guide polynucleotides can be associated with potentially harmful guide-dependent or guide-independent off-target base editing of DNA or RNA (**FIG. 24**). Such off-target base editing can be detrimental to the health of a subject administered a base editor system. For example, some off-target editing could lead to a disease in a subject, such as a cancer. Accordingly, experiments were undertaken to assess off-target editing of guide polynucleotides used in the above Examples.

Off-target editing was assessed for TSBTx3826, TSBTx3835, and TSBTx3837 guide polynucleotides *in silico* using rhAmpSeq™ panels of less than 500 sites (**Table 13**). Biologically relevant guide-dependent off-target loci were nominated for evaluation for off-target editing using rhAmpSeq™ (**Table 13**). A comparative, non-exhaustive, guide-dependent off-target assessment of gRNA:mRNA combinations was undertaken. The

following criteria were used for off-target site validation for the guide polynucleotides targeting CFB for base editing: 1) off-target site has an A>G edit in positions 4-9 of the target site that is significantly enriched in edited cells compared to untreated cells; 2) off-target edits is reproducible across replicates. Results of an assessment of off-target editing using these

5 criteria for guide polynucleotides containing different nucleotide modification schemes is summarized in **Table 14**. No off-target edits were predicted to affect splicing, no off-target edits were known to be pathogenic in ClinVar, which includes cancer driver mutations, and no off-target edit was a known variant in the UK Biobank (UKBB), gnomAD, or TOPMed

10 databases (**Table 15**). ClinVar is an NIH public archive of human genetic variation and associated phenotypes with supporting evidence. UKBB is a database of comprehensive medical record and genetic data from 500k individuals in the United Kingdom. The database gnomAD contains a collection of exome and genome sequences (~140k) to enable calculation of each gene's loss of function tolerance. The TOPMed database integrates -omics data with

15 molecular, behavioral, imaging, environmental, and clinical data to improve the prevention and treatment of heart, lung, blood, and sleep disorders.

Table 13. CFB rhAmpSeq panels

Target site	Sites Nominated	Sites Assessed
TSBTx3826	335	312 (93%)
TSBTx3835	284	251 (88%)
TSBTx3837	268	240 (90%)

Table 14. Off-target base editing assessment summary.

Target Site	gRNA mod sceme	Total number of off-target sites	Missense Variants	Pathogenic	Associated Gene in Cancer Census	Max edit frequency
TSBTx3826	End Mod	1	0	0	0	9.51
TSBTx3826	HM01	1	0	0	0	7.2
TSBTx3826	HM07	2	0	0	0	32.99
TSBTx3826	NLS	2	1	0	0	8.57
TSBTx3826	LONGEST	1	0	0	0	10.77
TSBTx3835	End Mod	0	0	0	0	0
TSBTx3837	End Mod	0	0	0	0	0

TSBTx3837	HM01	0	0	0	0	0
TSBTx3837	HM07	1	0	0	0	0.36
TSBTx3837	NLS	0	0	0	0	0
TSBTx3837	LONGEST	0	0	0	0	0

Table 15. Off-target base editing assessment summary.

Target Site	Genomic Coordinates	Off-target gene	Consequence	% Off-target editing (Lipofection)				
				End Mod	HM01	HM07	NLS	LONGEST
TSBTx3826	chr20:32088617-32088640(-)	HCK	Non-synonymous	.	.	.	0.20	.
	chrX:41238829-41238852(+)	.	Intergenic	9.51	7.20	32.99	7.57	10.77
	chr18:72730463-72730485(-)	.	Intergenic	.	.	2.22	.	.
TSBTx3837	chr10:29828002-29828024(-)	.	Intergenic	HM07: 0.36				

Table 15 (CONTINUED).

Target Site	Gene expressed in Liver/Spleen (TPM ≥ 1)	Off-target in Enhancer	Primary Disease Association of Gene	Gene Tolerant to Loss of Function	Gene Description
TSBTx3826	Liver, Spleen	n	Cancer	y	Src family of tyrosine kinases
	.	Liver	.	.	.
	.	n	.	.	.
TSBTx3837	.	n	.	.	.

5

OTHER EMBODIMENTS

From the foregoing description, it will be apparent that variations and modifications may be made to the aspects or embodiments described herein to adopt it to various usages and conditions. Such embodiments are also within the scope of the following claims.

10 The recitation of a listing of elements in any definition of a variable herein includes definitions of that variable as any single element or combination (or subcombination) of

listed elements. The recitation of an embodiment herein includes that embodiment as any single embodiment or in combination with any other embodiments or portions thereof.

All patents and publications mentioned in this specification are herein incorporated by reference to the same extent as if each independent patent and publication was specifically
5 and individually indicated to be incorporated by reference.

The disclosure may be related to International Patent Application No. PCT/US2023/068543, filed June 15, 2023, the entirety of which is incorporated herein by reference for all purposes.

CLAIMS

What is claimed:

1. A method of altering a nucleobase of a complement factor B (CFB) polynucleotide, the method comprising contacting the CFB polynucleotide with a base editor system comprising one or more guide polynucleotides, or one or more polynucleotides encoding the 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 polynucleotide encoding the base editor, wherein:
 - (a) said one or more guide polynucleotides targets said base editor to effect an alteration of a nucleobase of the CFB polynucleotide that:
 - i. disrupts a splice site in the CFB polynucleotide,
 - ii. alters a start codon in the CFB polynucleotide,
 - iii. alters a TATA box in the CFB polynucleotide, and/or
 - iv. introduces a new stop codon in the CFB polynucleotide;
 - (b) the deaminase domain comprises a TadA variant (TadA*) comprising an amino acid sequence having at least 90% sequence identity to the following TadA*7.10 amino acid sequence:

MSEVEFSHEYWMRHALTLAKRARDEREVPVGAVLVLNNRVIGEGWNRAIGLHDPTAHAEIMA
 LRQGGLVMQNYRLIDATLYVTFEPCVMCAGAMIHSRIGRVVFGVRNAKTGAAGSLMDVLHYP
 GMNHRVEITEGILADECAALLCYFFRMPRQVFNAQKKAQSSTD (SEQ ID NO: 1), or a fragment thereof lacking only the N-terminal methionine, wherein the TadA* further comprises a combination of amino acid alterations compared to the TadA*7.10 amino acid sequence selected from the group consisting of:

 - i. I76Y, V82T, Y123H, Y147T, and Q154S,
 - ii. Y123H, Y147R, and Q154R,
 - iii. I76Y, Y133H, Y147R, and Q154R,
 - iv. V82S, and Q164R,
 - v. I76Y, V82S, Y123H, Y147R, and Q154R, and
 - vi. I76Y, V82T, Y123H, Y147R, and Q154R; and/or
 - (c) the one or more guide polynucleotides comprises a nucleic acid sequence selected from CCUCAGAUGUCUAUGUGUUU (SEQ ID NO: 1524), UGCUUACAAUGACUGAGAUCU (SEQ ID NO: 1535), UUGCUCCTCCCAUGGCGUUGGA (SEQ ID NO: 3476),

CCCCAUGGCGUUGGAAGGCA (SEQ ID NO: 3443), and UGCUCCTCCCAUGGCGUUGGAA (SEQ ID NO: 3467) and/or comprising at least 10-23 contiguous nucleotides of a spacer nucleic acid sequence listed in any one of **Tables 2A to 2F**;

thereby altering the nucleobase of the CFB polynucleotide.

5

2. The method of claim 1, wherein the splice site is located near the 5' end of Exon 10, Exon 1, Exon 11, Exon 12, Exon 14, Exon 15, or Exon 16 of the CFB polynucleotide.

3. The method of claim 1, wherein the splice site is located near the 3' end of Exon 5, Exon 8, Exon 9, Exon 10, Exon 11, Exon 14, or Exon 18 of the CFB polynucleotide.

10

4. The method of claim 1, wherein the one or more guide polynucleotides comprises a spacer complementary to both a human CFB polynucleotide and a non-human primate CFB polynucleotide.

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5. The method of claim 1, wherein the one or more guide polynucleotides comprises a spacer complementary a human CFB polynucleotide.

6. The method of claim 1, wherein the one or more guide polynucleotides comprises a spacer complementary to a human CFB polynucleotide but not to a non-human primate CFB polynucleotide.

20

7. The method of claim 1, wherein the one or more guide polynucleotides comprise a spacer consisting of 20 or 21 nucleotides.

25

8. The method of claim 1, wherein the one or more guide polynucleotides comprise a spacer comprising a nucleotide sequence selected from the group consisting of:

CCUCAGAUGUCUAUGUGUUU (SEQ ID NO: 1524; TSBTx3826),

UGCUCCTCCCAUGGCGUUGGAA (SEQ ID NO: 3467; gRNA3657),

30 UUGCUCCTCCCAUGGCGUUGGA (SEQ ID NO: 3476; gRNA3658),

CCCCAUGGCGUUGGAAGGCA (SEQ ID NO: 3443; gRNA3660),

GCUUACAAUGACUGAGAUCU (SEQ ID NO: 1534; TSBTx3837),

UGC UUACAAUGACUGAGAUCU (SEQ ID NO: 1535; TSBTx3837) and
UCUCACCUCUGCAAGUAUUG (SEQ ID NO: 1529; TSBTx3835).

9. A method of altering a nucleobase of a complement factor B (CFB) polynucleotide,
5 the method comprising contacting the CFB polynucleotide with one or more guide
polynucleotides, or one or more polynucleotides encoding the 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, wherein:
- 10 (a) the deaminase domain comprises a cytidine deaminase or a TadA variant (TadA*)
comprising an amino acid sequence having at least 90% sequence identity to the following
TadA*7.10 amino acid sequence:
MSEVEFSHEYWMRHALTLAKRARDEREVPVGAVLVLNRRVIGEGWNRAIGLHDPTAHAEIMA
LRQGGLVMQNYRLIDATLYVTFEPCVMCAGAMIHSRIGRVVFGVRNAKTGAAGSLMDVLHYP
15 GMNHRVEITEGILADECAALLCYFFRMPRQVFNAQKKAQSSTD (SEQ ID NO: 1), or a
fragment thereof lacking only the N-terminal methionine, wherein the TadA* further
comprises a combination of amino acid alterations compared to the TadA*7.10 amino acid
sequence selected from the group consisting of:
- i. I76Y, V82T, Y123H, Y147T, and Q154S,
 - 20 ii. Y123H, Y147R, and Q154R,
 - iii. I76Y, Y133H, Y147R, and Q154R,
 - iv. V82S, and Q164R,
 - v. I76Y, V82S, Y123H, Y147R, and Q154R, and
 - vi. I76Y, V82T, Y123H, Y147R, and Q154R; and
- 25 (b) the one or more guide polynucleotides comprise a spacer comprising a nucleotide
sequence selected from the group consisting of CCUCAGAUGUCUAUGUGUUU (SEQ ID NO:
1524; TSBTx3826), UGCUC CCAUGGCGUUGGAA (SEQ ID NO: 3467; gRNA3657),
UUGCUC CCAUGGCGUUGGA (SEQ ID NO: 3476; gRNA3658),
CCCCAUGGCGUUGGAAGGCA (SEQ ID NO: 3443; gRNA3660),
30 GCUUACAAUGACUGAGAUCU (SEQ ID NO: 1534; TSBTx3837),
UGC UUACAAUGACUGAGAUCU (SEQ ID NO: 1535; TSBTx3837), and
UCUCACCUCUGCAAGUAUUG (SEQ ID NO: 1529; TSBTx3835);
thereby altering the nucleobase of the CFB polynucleotide.

10. The method of claim 1 or claim 9, wherein the deaminase domain is an adenosine deaminase comprising the TadA*7.10 amino acid sequence further comprising a combination of amino acid alterations selected from the group consisting of:
- 5 i. I76Y, V82T, Y123H, Y147T, and Q154S,
 - ii. Y123H, Y147R, and Q154R,
 - iii. I76Y, Y133H, Y147R, and Q154R,
 - iv. V82S, and Q164R,
 - v. I76Y, V82S, Y123H, Y147R, and Q154R, and
 - 10 vi. I76Y, V82T, Y123H, Y147R, and Q154R.
11. The method of claim 1 or claim 9, wherein the napDNAbp is a nickase.
12. The method of claim 11, wherein the napDNAbp binds a protospacer adjacent motif (PAM) selected from the group consisting of NGA, NGC, NGG, and NNNRRT, wherein “N” is any nucleotide and “R” is A or G.
13. The method of claim 12, wherein the napDNAbp is a Cas9 polypeptide.
14. The method of claim 1 or claim 9, wherein the one or more guide polynucleotides comprises a modified nucleotide.
15. The method of claim 14, wherein the one or more guide polynucleotides comprises a sequence selected from the group consisting of:
- 25 End-mod SpCas9 guide polynucleotide
mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUAGAGCUAGAAAUAGCAAGUAAAAUAAGGCU
AGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU (SEQ ID NO:
440);
- End-mod SaCas9 guide polynucleotide
- 30 mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUAGUACUCUGUAAUGAAAAUUACAGAAUCUA
CUAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU
(SEQ ID NO: 3128);
- HM01:
mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUAGAmGmCmUmAmGmAmAmUmAmGmCAAGU

UAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmG
mAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NO: 440);

HM07:

5 mNsmNsmNsmNmNmNmNmNmNmNNNNNNNNNNmGUUUUAGmAmGmCmUmAmGmAmAmAmUm
AmGmCmAmAGUUmAAmAAmUAmAmGmGmCmUmAGUmCmCGUUAmUmCAAmCmUmUmGmAmAm
AmAmAmGmUmGGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NO:
440);

NLS (bpsv40):

10 mNsmNsmNsNNNNNNNNNNNNNNNNNNNGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCU
AGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsmU-NHC6-CrossL-
ac- CKRTADGSEFESPKKKRKV (SEQ ID NOs: 440 and 446);

LONGEST:

mNsmNsmNsNNNNNNNNNNNNNNNNNNNGUUUUAGAmGmCmCmGmGmCmGmGmAmAmAmCmGmC
mCmGmGmCAAGUUAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGUGmG
15 mCmAmCmCmGmAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NO: 445);

NLS + LONGEST :

mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUAGAmGmCmCmGmGmCmGmGmAmAmAmCmGmC
mCmGmGmCAAGUUAUUAAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmG
mGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmUsmUsmUsmU-NHC5-CrossL-
20 CKRTADGSEFESPCKKKRKV (SEQ ID NOs: 445 and 446); and

LONGEST + GOLD:

mNsmNsmNsNNNNNNNNNNNNNNNNNNNGUUUUAGAmGmCmCmGmGmCmGmGmAmAmAmCmGmC
mCmGmGmCAAGUUAUUAAAGGCUAGUCCGUUAmUmCAAmCmUmUGGACUUCGGUCCmAmAm
GUGGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NO: 447);

25 wherein “N” represents any nucleotide, “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), and wherein the number of N nucleotides is between 15 and 25.

30

16. The method of claim 1 or claim 9, wherein the CFB polynucleotide is in a cell.

17. The method of claim 16, wherein the cell is a mammalian cell.

18. The method of claim 17, wherein the cell is a retinal cell or other cell of the eye, a nerve cell, or a hepatocyte.

5 19. A cell produced by the method of any one of claims 16-18.

20. 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 comprising at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 contiguous nucleobases of a spacer comprising a nucleotide sequence selected from CCUCAGAUGUCUAUGUGUUU (SEQ ID NO: 1524), UGCUUACAAUGACUGAGAUCU (SEQ ID NO: 1535), UUGCUCUCCCAUGGCGUUGGA (SEQ ID NO: 3476), CCCCAUGGCGUUGGAAGGCA (SEQ ID NO: 3443), and UGCUCUCCCAUGGCGUUGGAA (SEQ ID NO: 3467) and/or listed in **Table 2A to 2F**, or one or more polynucleotides encoding the one or more guide polynucleotides.

21. The base editor system of claim 20, wherein the deaminase domain comprises a TadA variant (TadA*) comprising an amino acid sequence having at least 90% sequence identity to the following TadA*7.10 amino acid sequence:

20 MSEVEFSHEYWMRHALTLAKRARDEREVPVGAVLVLNNRVIGEGWNRAIGLHDPTAHAEIMA
LRQGGLVMQNYRLIDATLYVTTFEPCVMCAGAMIHRSRIGRVVFGVRNAKTGAAGSLMDVLHYP
GMNHRVEITEGILADECAALLCYFFRMPRQVFNAQKKAQSSTD (SEQ ID NO: 1), wherein the TadA* further comprises a combination of amino acid alterations compared to the TadA*7.10 amino acid sequence selected from the group consisting of:

- 25 i. Y123H, Y147R, and Q154R,
ii. I76Y, Y133H, Y147R, and Q154R,
iii. V82S, and Q164R,
iv. I76Y, V82S, Y123H, Y147R, and Q154R,
v. I76Y, V82T, Y123H, Y147R, and Q154R, and
30 vi. I76Y, V82T, Y123H, Y147T, and Q154S; or
wherein the deaminase domain comprises a cytidine deaminase.

22. The base editor system of claim 20, wherein the one or more guide polynucleotides comprise a spacer comprising a nucleotide sequence selected from the group consisting of: CCUCAGAUGUCUAUGUGUUU (SEQ ID NO: 1524; TSBTx3826), UGCUCCTCAUGGCGUUGGAA (SEQ ID NO: 3467; gRNA3657),
- 5 UUGCUCCTCAUGGCGUUGGA (SEQ ID NO: 3476; gRNA3658), CTTCAUGGCGUUGGAAGGCA (SEQ ID NO: 3443; gRNA3660), GCUUACAAUGACUGAGAUCU (SEQ ID NO: 1534; TSBTx3837), UGCUUACAAUGACUGAGAUCU (SEQ ID NO: 1535; TSBTx3837), and UCUCACCUCUGCAAGUAUUG (SEQ ID NO: 1529; TSBTx3835).
- 10
23. The base editor system of claim 20, wherein the napDNAbp is a Cas9 nickase polypeptide that binds a protospacer adjacent motif (PAM) selected from the group consisting of NGA, NGC, NGG, and NNNRRT, wherein "N" is any nucleotide and "R" is A or G.
- 15
24. The base editor system of claim 20, the one or more guide polynucleotides comprises a sequence selected from the group consisting of:
- End-mod SpCas9 guide polynucleotide
mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUAGAGCUAGAAAUAGCAAGUAAAAUAAGGCU
AGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU (SEQ ID NO:
- 20 440);
- End-mod SaCas9 guide polynucleotide
mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUAGUACUCUGUAAUGAAAAUUACAGAAUCUA
CUAAAAACAAGGCAAAAUGCCGUGUUUAUCUCGUCAACUUGUUGGCGAGAUsmUsmUsmU
(SEQ ID NO: 3128);
- 25 HM01:
mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUAGAmGmCmUmAmGmAmAmUmAmGmCAAGU
UAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmG
mAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NO: 440);
- HM07:
30 mNsmNsmNsmNmNmNmNmNmNmNNNNNNNNNNNmGUUUUAGmAmGmCmUmAmGmAmAmUm
AmGmCmAmAGUUmAAmAAmUAmAmGmGmCmUmAGUmCmCGUUmUmCAAmCmUmUmGmAmAm
AmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NO:
440);

NLS (bpsv40):

mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUUAGAGCUAGAAAUAGCAAGUAAAAUAAGGCU
AGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsmU-NHC6-CrossL-
ac- CKRTADGSEFESPKKKRKV (SEQ ID NOs: 440 and 446);

5 LONGEST:

mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUUAGAmGmCmCmGmGmCmGmGmAmAmAmCmGmC
mCmGmGmCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGUGmG
mCmAmCmCmGmAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NO: 445);

NLS + LONGEST :

- 10 mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUUAGAmGmCmCmGmGmCmGmGmAmAmAmCmGmC
mCmGmGmCAAGUUAUUAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmG
mGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmUsmUsmUsmU-NHC5-CrossL-
CKRTADGSEFESPKKKRKV (SEQ ID NOs: 445 and 446); and

LONGEST + GOLD:

- 15 mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUUAGAmGmCmCmGmGmCmGmGmAmAmAmCmGmC
mCmGmGmCAAGUUAUUAAUAAGGCUAGUCCGUUAUmUmCAAmCmUmUGGACUUCGGUCCmAmAm
GUGGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NO: 447);

- wherein “N” represents any nucleotide, “mN” indicates a 2'-OMe modification of the
nucleotide “N”, and “Ns” indicates that the nucleotide “N” is linked to the following
20 nucleotide by a phosphorothioate (PS), and wherein the number of N nucleotides is between
15 and 25.

25. A polynucleotide encoding the base editor system of any one of claims 20-24, or a
component thereof.
- 25
26. A vector comprising the base editor system of any one of claims 20-24, or the
polynucleotide of claim 25.
27. A lipid nanoparticle comprising the base editor system of any one of claims 20-24, or
30 the polynucleotide of claim 25.

28. A pharmaceutical composition comprising an effective amount of the base editor system of any one of claims 20-24 or the vector of claim 26, or the lipid nanoparticle of claim 27 and a pharmaceutically acceptable excipient.
- 5 29. A kit comprising the base editor system of any one of claims 20-24, the vector of claim 26, the lipid nanoparticle of claim 27, or the pharmaceutical composition of claim 28, disposed within a container.
30. A guide polynucleotide comprising a sequence listed in any one of **Tables 1A to 2F**.
- 10 31. 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:
- 15 (a) the deaminase domain is a cytidine deaminase or comprises a TadA variant (TadA*) comprising an amino acid sequence having at least 90% sequence identity to the following TadA*7.10 amino acid sequence:
- MSEVEFSHEYWMRHALTLAKRARDEREVPVGAVLVLNNRVIGEGWNRAIGLHDPTAHAEIMA
LRQGGLVMQNYRLIDATLYVTTFEPCVMCAGAMIHSRIGRVVFGVRNAKTGAAGSLMDVLHYP
20 GMNHRVEITEGILADECAALLCYFFRMPRQVFNAQKKAQSSTD (SEQ ID NO: 1), wherein the TadA* further comprises a combination of amino acid alterations compared to the TadA*7.10 amino acid sequence selected from the group consisting of:
- i. I76Y, V82T, Y123H, Y147T, and Q154S,
ii. Y123H, Y147R, and Q154R,
25 iii. I76Y, Y133H, Y147R, and Q154R,
iv. V82S, and Q164R,
v. I76Y, V82S, Y123H, Y147R, and Q154R, and
vi. I76Y, V82T, Y123H, Y147R, and Q154R;
- (b) the one or more guide polynucleotides comprise a spacer comprising a nucleotide
30 sequence selected from the group consisting of: CCUCAGAUGUCUAUGUGUUU (SEQ ID NO: 1524; TSBTx3826), UGCUCGCCAUGGCGUUGGAA (SEQ ID NO: 3467; gRNA3657),
UUGCUCGCCAUGGCGUUGGA (SEQ ID NO: 3476; gRNA3658),
CCCCAUGGCGUUGGAAGGCA (SEQ ID NO: 3443; gRNA3660),

GCUUACAAUGACUGAGAUCU (SEQ ID NO: 1534; TSBTx3837),
 UGCUUACAAUGACUGAGAUCU (SEQ ID NO: 1535; TSBTx3837), and
 UCUCACCUCUGCAAGUAUUG (SEQ ID NO: 1529; TSBTx3835);

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

End-mod SpCas9 guide polynucleotide

mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUAGAGCUAGAAAUAGCAAGUAAAAUAAGGCU
 AGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU (SEQ ID NO:
 440),

- 10 HM01:

mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUAGAmGmCmUmAmGmAmAmUmAmGmCAAGU
 UAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmG
 mAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NO: 440), and

NLS (bpsv40):

- 15 mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUAGAGCUAGAAAUAGCAAGUAAAAUAAGGCU
 AGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsmU-NHC6-CrossL-
 ac- CKRTADGSEFESPKKKRKV (SEQ ID NOs: 440 and 446),

- wherein “N” represents any nucleotide, “mN” indicates a 2'-OMe modification of the
 nucleotide “N”, and “Ns” indicates that the nucleotide “N” is linked to the following
 20 nucleotide by a phosphorothioate (PS), and wherein the number of N nucleotides is between
 15 and 25; and

(d) the napDNAbp is an spCas9 nickase polypeptide that binds a protospacer adjacent
 motif (PAM) selected from the group consisting of NGA, NGC, and NGG, wherein “N” is any
 nucleotide.

25

32. A lipid nanoparticle comprising the base editor system of claim 31.

33. A composition comprising:

- a) a polynucleotide encoding a base editor comprising a nucleic acid programmable
 30 DNA binding protein (napDNAbp) domain and a deaminase domain, wherein the deaminase
 domain is a cytidine deaminase or comprises a TadA variant (TadA*) comprising an amino
 acid sequence having at least 90% sequence identity to the following TadA*7.10 amino acid
 sequence:

MSEVEFSHEYWMRHALTLAKRARDEREVPVGAVLVLNNRVIGEGWNRAIGLHDPTAHAEIMA
LRQGGLVMQNYRLIDATLYVTFEPCVMCAGAMIHSRIGRVVFGVRNAKTGAAGSLMDVLHYP
GMNHRVEITEGILADECAALLCYFFRMPRQVFNAQKKAQSSTD (SEQ ID NO: 1), wherein
the TadA* further comprises a combination of amino acid alterations compared to the

5 TadA*7.10 amino acid sequence selected from the group consisting of:

i. I76Y, V82T, Y123H, Y147T, and Q154S,

ii. Y123H, Y147R, and Q154R,

iii. I76Y, Y133H, Y147R, and Q154R,

iv. V82S, and Q164R,

10 v. I76Y, V82S, Y123H, Y147R, and Q154R, and

vi. I76Y, V82T, Y123H, Y147R, and Q154R; and

b) a guide RNA comprises a spacer comprising a nucleotide sequence selected from
the group consisting of: CCUCAGAUGUCUAUGUGUUU (SEQ ID NO: 1524; TSBTx3826),
UGCUCUCCCAUGGCGUUGGAA (SEQ ID NO: 3467; gRNA3657),

15 UUGCUCUCCCAUGGCGUUGGA (SEQ ID NO: 3476; gRNA3658),

CCCCAUGGCGUUGGAAGGCA (SEQ ID NO: 3443; gRNA3660),

GCUUACAAUGACUGAGAUCU (SEQ ID NO: 1534; TSBTx3837),

UGC UUACAAUGACUGAGAUCU (SEQ ID NO: 1535; TSBTx3837), and

UCUCACCUCUGCAAGUAUUG (SEQ ID NO: 1529; TSBTx3835) and/or comprising at least

20 10-23 contiguous nucleotides of a spacer nucleic acid sequence listed in any one of **Tables
2A to 2F**.

34. The composition of claim 33, wherein the guide RNA comprises a sequence selected
from the group consisting of:

25 End-mod SpCas9 guide polynucleotide

mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUUAGAGCUAGAAAUAGCAAGUAAAAUAAGGCU
AGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU (SEQ ID NO:
440),

HM01:

30 mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUUAGAmGmCmUmAmGmAmAmUmAmGmCAAGU
UAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmG
mAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NO: 440), and

NLS (bpsv40):

mNsmNsmNsNNNNNNNNNNNNNNNGUUUAGAGCUAGAAAUAGCAAGUAAAAUAAGGCU
AGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsmU-NHC6-CrossL-
ac- CKRTADGSEFESPKKKRKV (SEQ ID NOs: 440 and 446),

- 5 wherein “N” represents any nucleotide, “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), and wherein the number of N nucleotides is between 15 and 25.

- 10 35. The composition of claim 33, wherein the polynucleotide is an mRNA.

36. The composition of any one of claims 33-35 formulated in a lipid nanoparticle (LNP).

37. A lipid nanoparticle (LNP) composition comprising:

- 15 a) an mRNA encoding a base editor comprising a nucleic acid programmable DNA binding protein (napDNAbp) domain and a deaminase domain, wherein the deaminase domain is a cytidine deaminase or comprises a TadA variant (TadA*) comprising an amino acid sequence having at least 90% sequence identity to the following TadA*7.10 amino acid sequence:
- 20 MSEVEFSHEYWMRHALTLAKRARDEREVPVGAVLVLNNRVIGEGWNRAIGLHDPTAHAEIMA
LRQGGLVMQNYRLIDATLYVTFEPCVMCAGAMIHSRIGRVVFGVRNAKTGAAGSLMDVLHYP
GMNHRVEITEGILADECAALLCYFFRMPRQVFNAQKKAQSSTD (SEQ ID NO: 1), wherein the TadA* further comprises a combination of amino acid alterations compared to the TadA*7.10 amino acid sequence selected from the group consisting of:

- 25 i. I76Y, V82T, Y123H, Y147T, and Q154S,
 ii. Y123H, Y147R, and Q154R,
 iii. I76Y, Y133H, Y147R, and Q154R,
 iv. V82S, and Q164R,
 v. I76Y, V82S, Y123H, Y147R, and Q154R, and
30 vi. I76Y, V82T, Y123H, Y147R, and Q154R; and

- b) a guide RNA comprises a spacer comprising a nucleotide sequence selected from the group consisting of: CCUCAGAUGUCUAUGUGUUU (SEQ ID NO: 1524; TSBTx3826), UGCUCCCCAUGGCGUUGGAA (SEQ ID NO: 3467; gRNA3657),

- UUGCUCUCCCCAUGGCGUUGGA (SEQ ID NO: 3476; gRNA3658),
 CCCC AUGGCGUUGGAAGGCA (SEQ ID NO: 3443; gRNA3660),
 GCUUACAAUGACUGAGAUCU (SEQ ID NO: 1534; TSBTx3837),
 UGCUUACAAUGACUGAGAUCU (SEQ ID NO: 1535; TSBTx3837), and
 5 UCUCACCUCUGCAAGUAUUG (SEQ ID NO: 1529; TSBTx3835) and/or comprising at least
 10-23 contiguous nucleotides of a spacer nucleic acid sequence listed in any one of **Tables
 2A to 2F**.

38. The LNP composition of claim 37, wherein the guide RNA comprises a sequence
 10 selected from the group consisting of:
 End-mod SpCas9 guide polynucleotide
 mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCU
 AGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU (SEQ ID NO:
 440),
 15 HM01:
 mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUUAGAmGmCmUmAmGmAmAmUmAmGmCAAGU
 UAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmG
 mAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NO: 440), and
 NLS (bpsv40):
 20 mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCU
 AGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsmU-NHC6-CrossL-
 ac- CKRTADGSEFESPKKKRKV (SEQ ID NOs: 440 and 446),
 wherein “N” represents any nucleotide, “mN” indicates a 2'-OMe modification of the
 nucleotide “N”, and “Ns” indicates that the nucleotide “N” is linked to the following
 25 nucleotide by a phosphorothioate (PS), and wherein the number of N nucleotides is between
 15 and 25.

39. A method of treatment comprising administering to a subject a lipid nanoparticle
 (LNP) compositing comprising:
 30 a) an mRNA encoding a base editor comprising a nucleic acid programmable DNA
 binding protein (napDNAbp) domain and a deaminase domain, wherein the deaminase
 domain is a cytidine deaminase or comprises a TadA variant (TadA*) comprising an amino
 acid sequence having at least 90% sequence identity to the following TadA*7.10 amino acid

sequence:

MSEVEFSHEYWMRHALTLAKRARDEREVPVGAVLVNNRVIGEGWNRAIGLHDPTAHAEIMA
LRQGGLVMQNYRLIDATLYVTFEPCVMCAGAMIHSRIGRVVFGVRNAKTGAAGSLMDVLHYP
GMNHRVEITEGILADECAALLCYFFRMPRQVFNAQKKAQSSTD (SEQ ID NO: 1), wherein

- 5 the TadA* further comprises a combination of amino acid alterations compared to the
TadA*7.10 amino acid sequence selected from the group consisting of:

- i. I76Y, V82T, Y123H, Y147T, and Q154S,
- ii. Y123H, Y147R, and Q154R,
- iii. I76Y, Y133H, Y147R, and Q154R,
- 10 iv. V82S, and Q164R,
- v. I76Y, V82S, Y123H, Y147R, and Q154R, and
- vi. I76Y, V82T, Y123H, Y147R, and Q154R; and

- b) a guide RNA comprises a spacer comprising a nucleotide sequence selected from
the group consisting of: CCUCAGAUGUCUAUGUGUUU (SEQ ID NO: 1524; TSBTx3826),
15 UGCUCUCCCAUGGCGUUGGAA (SEQ ID NO: 3467; gRNA3657),
UUGCUCUCCCAUGGCGUUGGA (SEQ ID NO: 3476; gRNA3658),
CCCCAUGGCGUUGGAAGGCA (SEQ ID NO: 3443; gRNA3660),
GCUUACAAUGACUGAGAUCU (SEQ ID NO: 1534; TSBTx3837),
UGC UUACAAUGACUGAGAUCU (SEQ ID NO: 1535; TSBTx3837), and
20 UCUCACCUCUGCAAGUAUUG (SEQ ID NO: 1529; TSBTx3835) and/or comprising at least
10-23 contiguous nucleotides of a spacer nucleic acid sequence listed in any one of **Tables
2A to 2F**.

40. The method of claim 39, wherein the guide RNA comprises a sequence selected from
25 the group consisting of:

End-mod SpCas9 guide polynucleotide

mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCU
AGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUsmUsmUsmU (SEQ ID NO:
440),

- 30 HM01:

mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUUAGAmGmCmUmAmGmAmAmUmAmGmCAAGU
UAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmGmUmGmGmCmAmCmCmG
mAmGmUmCmGmGmUmGmCmUsmUsmUsmU (SEQ ID NO: 440), and

NLS (bpsv40):

mNsmNsmNsNNNNNNNNNNNNNNNNNGUUUUAGAGCUAGAAAUAGCAAGUUAUUAAUAAGGCU
AGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCmUsmUsmUsmU-NHC6-CrossL-
ac- CKRTADGSEFESPKKKRKV (SEQ ID NOs: 440 and 446),

- 5 wherein “N” represents any nucleotide, “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), and wherein the number of N nucleotides is between 15 and 25.

10