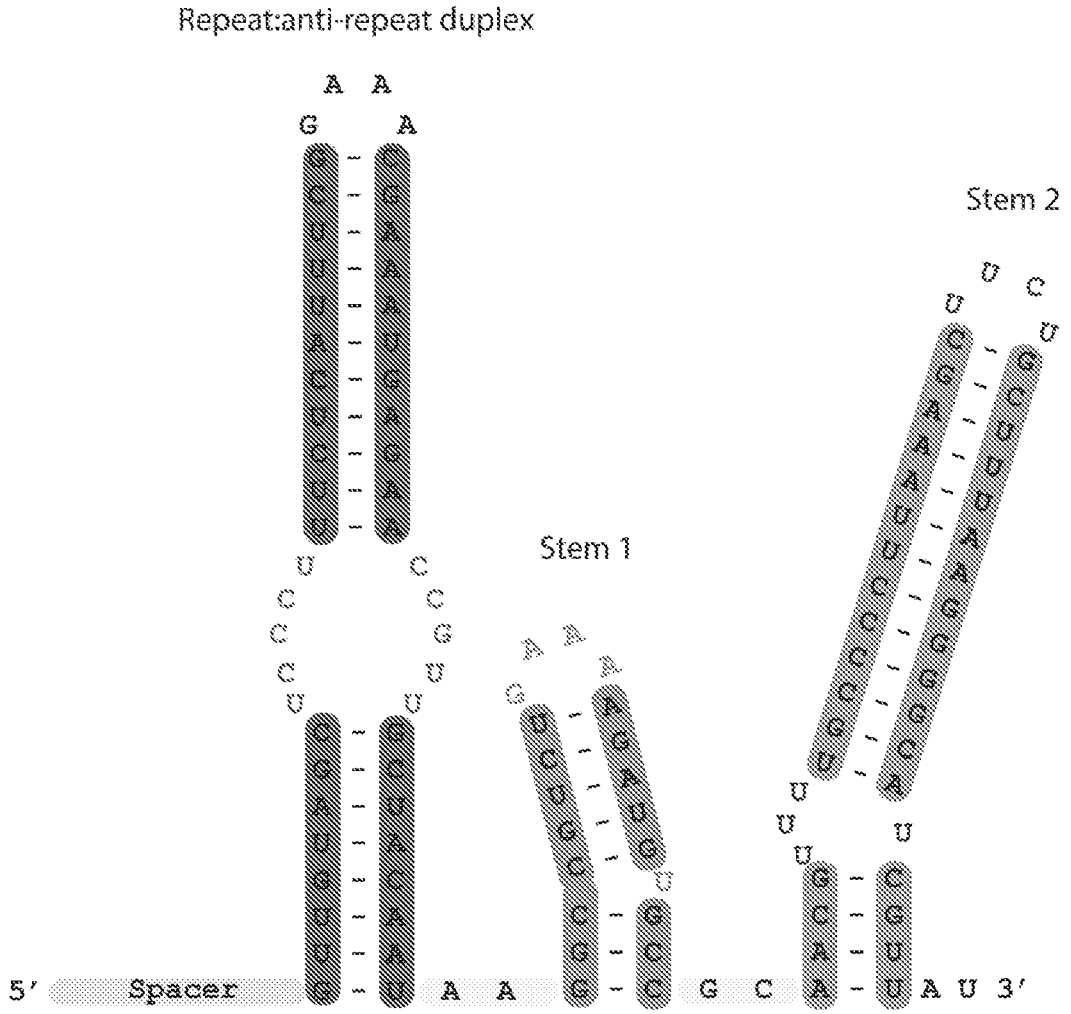


Figure 1

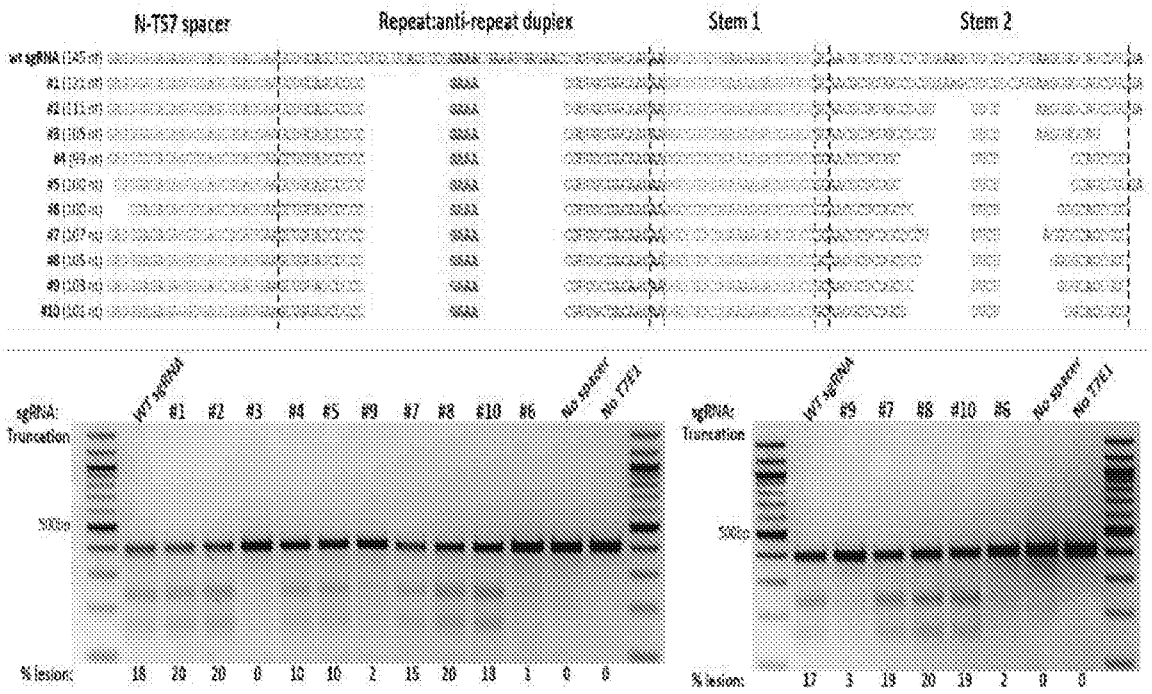

N-TS7 spacer
Repeat:anti-repeat duplex
Stem 1
Stem 2
sgRNA:
Truncation
500bp
% lesion:
WT sgRNA
#1
#2
#3
#4
#5
#9
#7
#8
#10
#6
No spacer
No T7E1
18 20 20 8 10 10 2 15 20 13 1 0 0
17 3 19 20 19 2 0 0

Figure 2

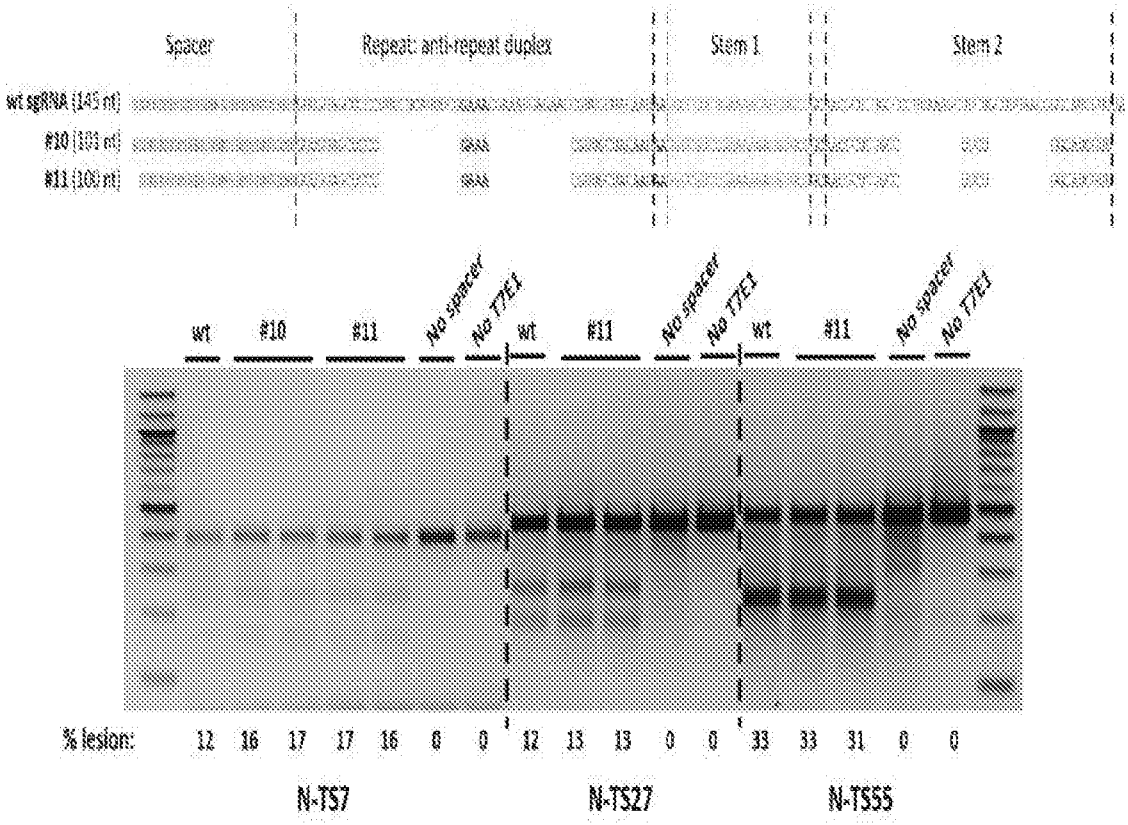

Spacer
Repeat: anti-repeat duplex
Stem 1
Stem 2
wt sgRNA (145 nt)
#10 (101 nt)
#11 (100 nt)
wt
#10
#11
No spacer
No T7E1
wt
#11
No spacer
No T7E1
wt
#11
No spacer
No T7E1
% lesion:
12 16 17 17 16 0 0 12 13 13 0 0 33 33 31 0 0
N-TS7
N-TS27
N-TS55

Figure 3

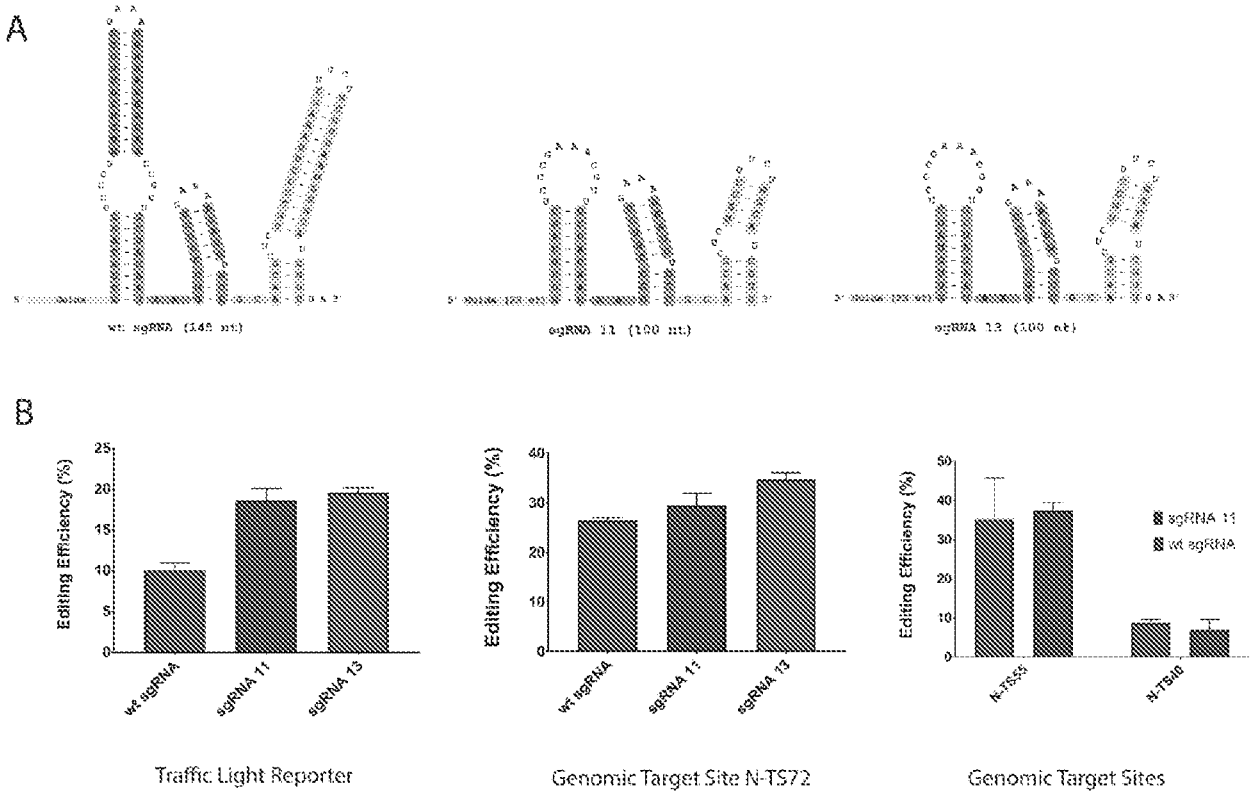
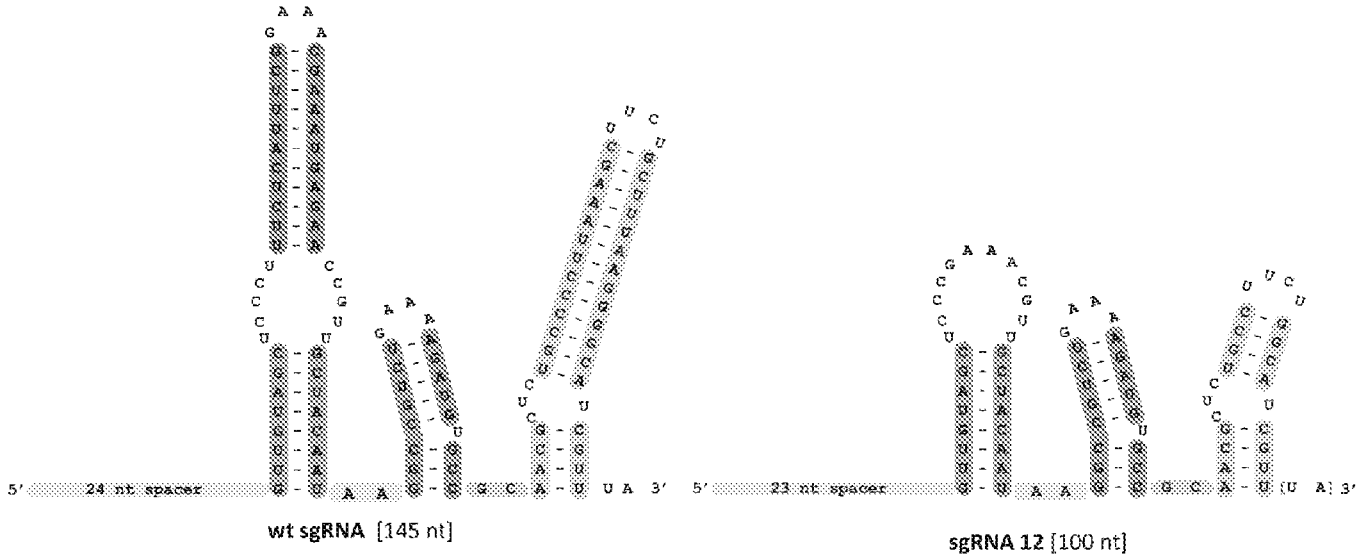

A
wt sgRNA (148 nt)
sgRNA 11 (100 nt)
sgRNA 13 (100 nt)
B
Editing Efficiency (%)
wt sgRNA
sgRNA 11
sgRNA 13
Traffic Light Reporter
Genomic Target Site N-TS72
N-TS55
N-TS48
Genomic Target Sites

Figure 4

C



D

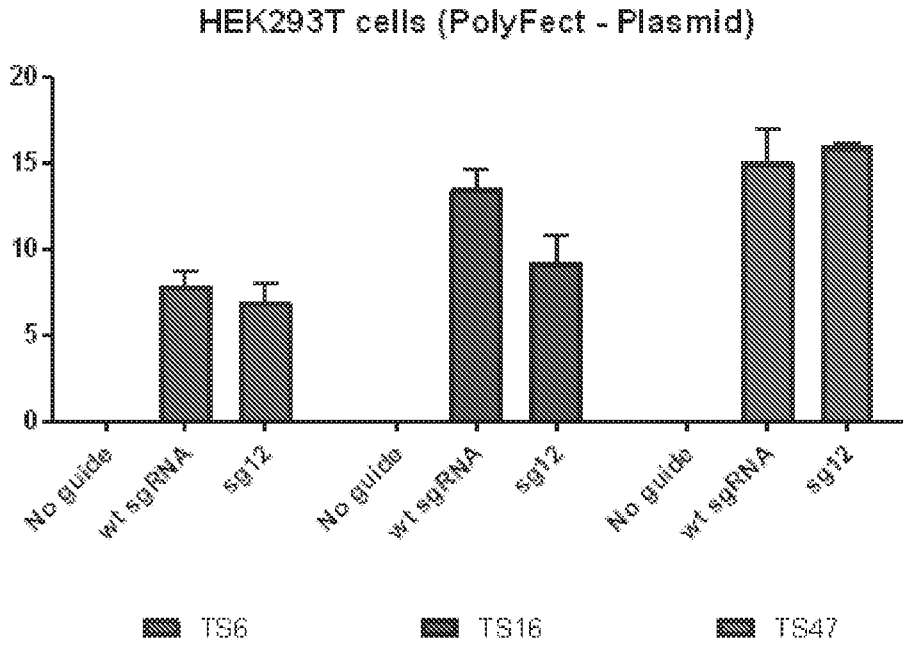


Figure 4 (cont'd)

E

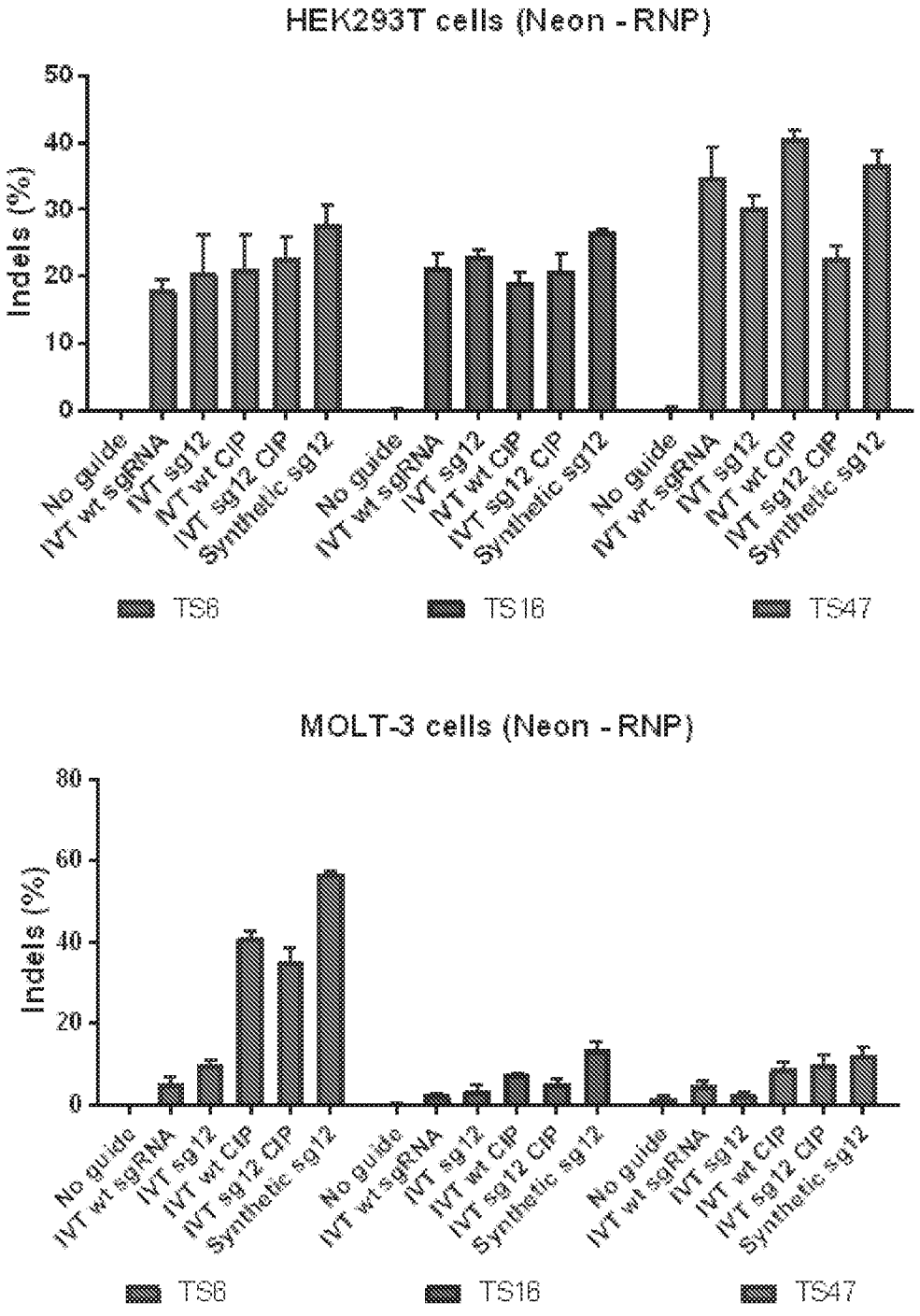


Figure 4 (cont'd)

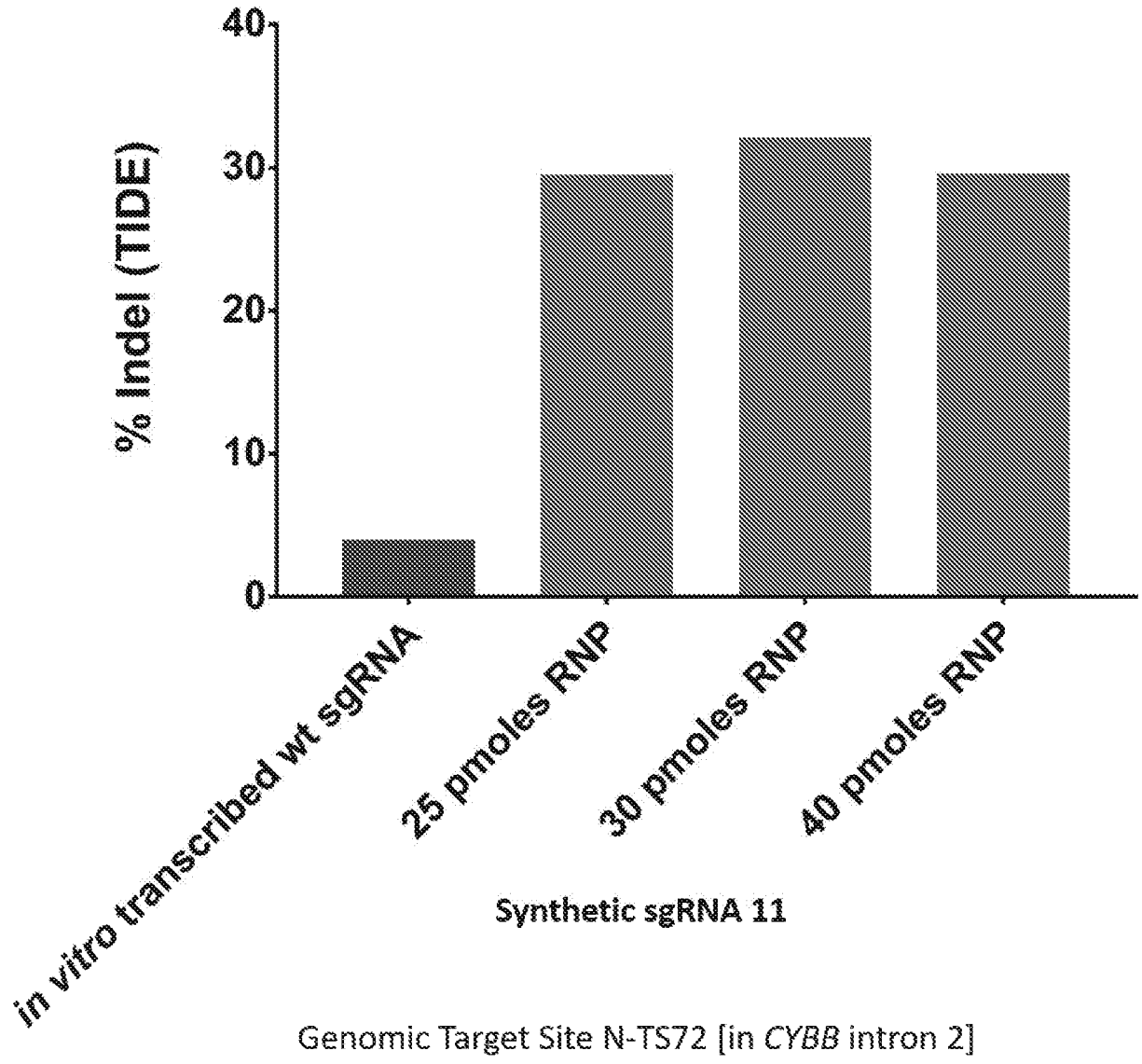
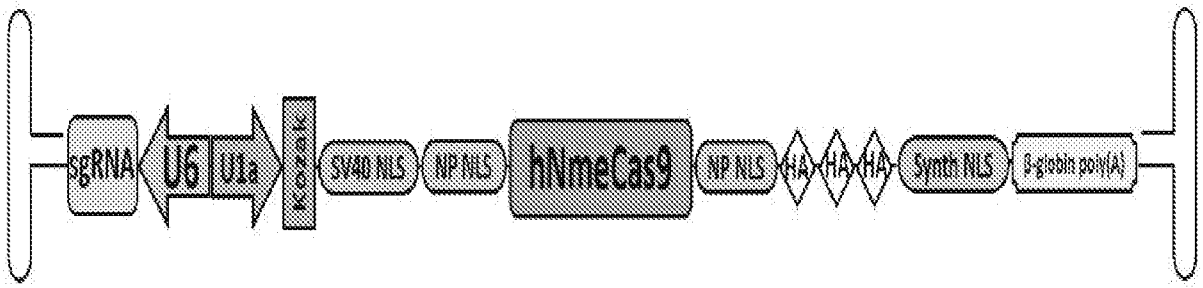
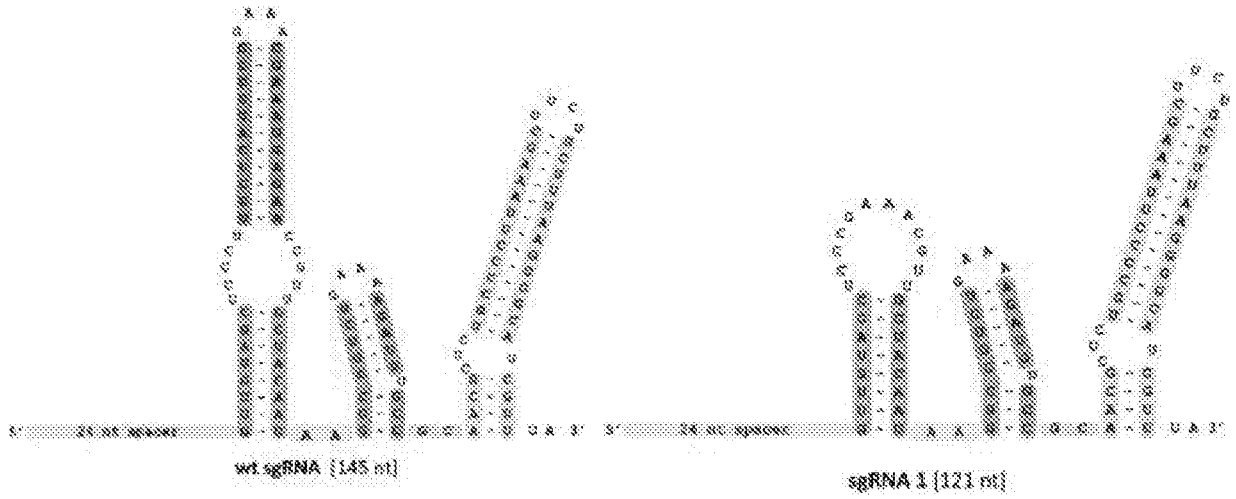

40
30
20
10
0
% Indel (TIDE)
in vitro transcribed wt sgRNA
25 pmoles RNP
30 pmoles RNP
40 pmoles RNP
Synthetic sgRNA 11
Genomic Target Site N-TS72 [in CYBB intron 2]

Figure 5

A


sgRNA
U6
U1a
Kozak
SV40 NLS
NP NLS
hNmeCas9
NP NLS
HA
HA
HA
Synth NLS
B-globin poly(A)

B


wt sgRNA (145 nt)
sgRNA 1 (121 nt)

C

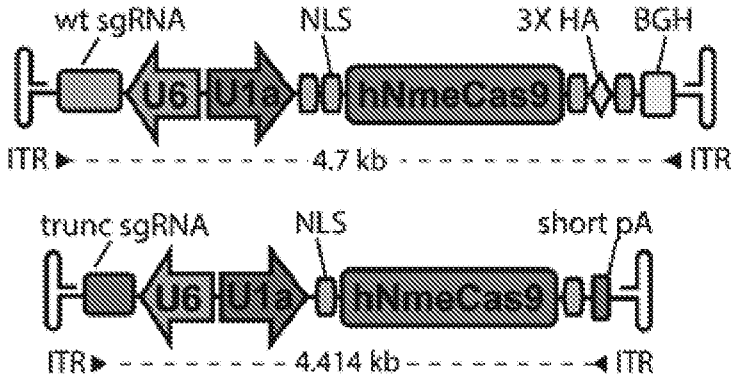

wt sgRNA
NLS
3X HA
BGH
U6
U1a
hNmeCas9
ITR
4.7 kb
ITR
trunc sgRNA
NLS
short pA
U6
U1a
hNmeCas9
ITR
4.414 kb
ITR

Figure 6

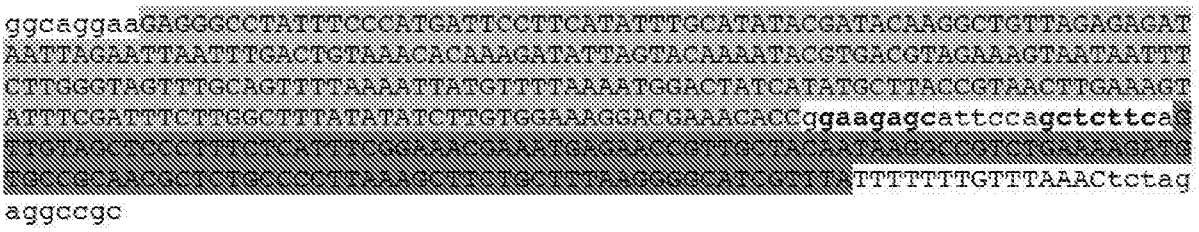

ggcaggaaGACGGCCTATTTCCCATGATTCCTTCATATTTGCATATACGATACAAGGCTGTTAGAGAGAT
AATTAGAATTAATTTGACTGTAAACACAAAGATATTAGTACAAAATACGTGACGTAGAAAGTAATAATTT
CTTGGGTAGTTTGCAGTTTTAAAATTATGTTTTAAAATGGACTATCATATGCTTACCGTAACTTGAAAGT
ATTTCGATTTCTTGGCTTTATATATCTTGTGGAAAGGACGAAACACCggaagagcattccagctcttca
TTTTTTTTGTTTAAACtctag
aggccgc

Figure 7

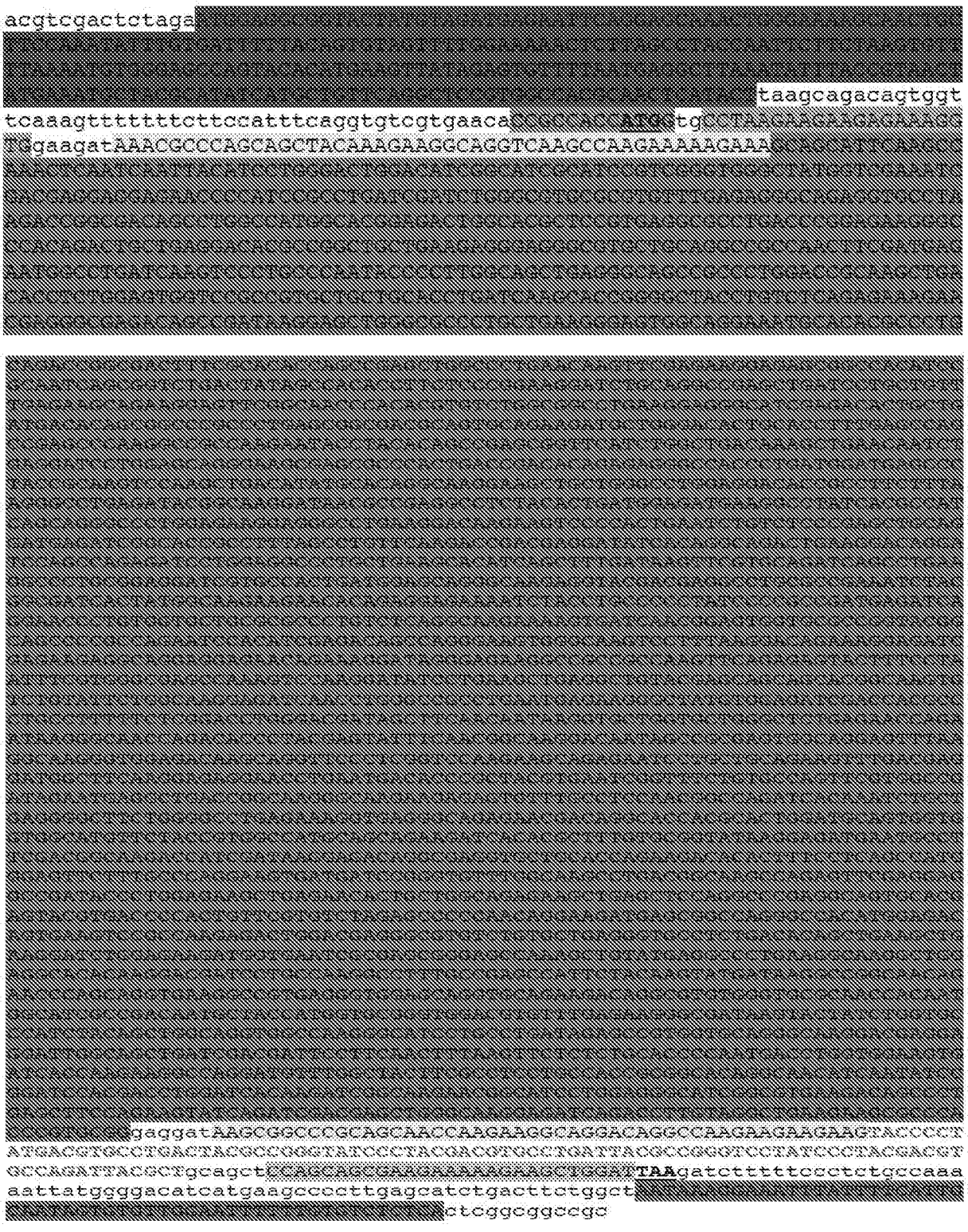


Figure 8

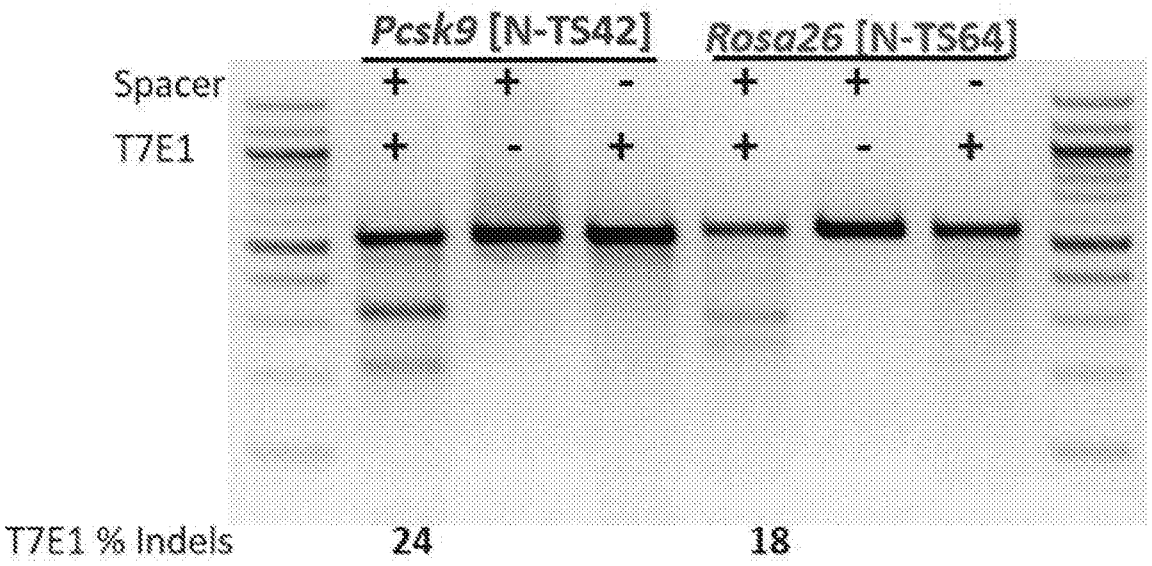


Figure 9

Pcsk9

TGGCGTGATCTCCCGGCCCCCAGGCGTC*CAGTACCCACACCCCCAGAA*GGCTTCCACCTTCACGTGGACGC
GCAGGCTGCCGGTG*GGCTCCCGTTCTCTCTCTCT*TTCTGAGGCTAGAGGACTGAGCCAGTCCTTGGCTCC
CCAGAGACATCACGGCCCGCAGCCCCCGGAGCCAAGTGCCCCGAGTCCCAGGCGTCCATGTCCTTCCCGAG
GCCGCGCGCACCTCTCCTCGCCCCGATGGGCACCCACTGCTCTGCGTGGCTGCGGTGGCCGCTGTTGCCG
CTGTTGCCGCCGCTGCTGCTGCTGTTGCTGCTACTGTGCCCCACCGGCGCTGGTGCCCAGGACGAGGATG
GAGATTATGAAGAGCTGATGCTCGCCCTCCCGTCCCAGGAGGATGGCCTGGCTGATGAGGCCGCACATGT
GGCCACCGCCACCTTCCGCCGTTGCTCCAAGGTATGGGTGCCAGGCAACGGCGTTGCTTTGGGGTTGGGG
TGATGCTCTTCGGGGGTCTTCTCTGCTCATCTAGCCGTCTGGTGGTCTC*TAAGTGCAGCCCTGAGGTG*CG
GGAGGCGAGGGCAAGACTTAGTGCTCAGCTGCACCTTGTGGCACAGAGTGATGGGGGAGGCCACGTGCTA
AAGGCACTGCGGGGCTTGGTTCCAAAAGTGTGAGGCGGGGAGCGGGCTACCAGTGTGGTCATGCAGAAAA
CGTGTCCTCCGAAGTAAAGTGGCATCGGGAGGCTGAGAACTCTAGTGGCACATCTTTCTCAACTGGTCAT
CCAGCAGTCATCCTGGGTGCCTGTTGGGGTTC*TGTAGGCCTCGATTTAGCGGAAGGGTGTCAGGG*

Rosa26

GGAAAGGGAAAATGCCAATGCTCTGTC*TAGGGGTTGGATAAGCCAGT*ATAATAAATGAAAATGGGGCTAA
AATGAGTGTTCTAAAATACCTTTTGATAAGGCTGCAGAAGGAGCGGGAGAAATGGATATGAAGTACTGGG
CTCTTTAAAAATGATTAAAATTCTGCTTACATAGTCTAACTCGCGACACTGTAATTTCATACTGTAGTAA
GGATCTCAAGCAGGAGAGTATAAAACTCGGGTGAGCATGTCTTTAATCTACCTCGATGGAAAATACTCCG
AGGCGGATCACAA*GCAATAATAACCTTTAGTTTTTGCTGC*ATAAAACCCCAGATGACTACCTATCCTCCCA
TTTTCCTTATTTGCCCCTATTAAAAAACTTCCCGACAAAACCGAAAATCTGTGGGAAGTCTTGTCCCTCC
AATTTTACACCTGTTCAATTCCCCTGCAGGACAACGCCCACACACCAGGTTAGCCTTTAAGCCTGCCCAG
AAGACTCCCGCCCATCTTCTAGAAAGACTGGAGTTGCAGATCACGAGGGAAGAGGGGGAAGGGATTCTCC
CAGGCCCAGGGCGGTCCTCAGAAGCCAGGAGGCAGCAGAGAACTCCCAGAAAGGTATTGCAACACTCCCC
TCCCCCCTCCGGAGAAGGGTGCGGCCTTCTCCCCGCCTACTCCACTGCAGCTCCCTTACTGATAACAACT
CAGAGCGACTTTGGGAGAGCAAGTGCTTCCTGC*CTCCAAAACAGCCCAACTGAGCCCTCGCTCCTTCCCT*
CCACTCCCCGGAGTGCGCGATGGAGGTCTGGCTCAGCACGCCCCTCTTGAGGCAACT*CAAGTCGGAAACG*
*TGCTTG*CACCCGCCCCGCAGCCG

Figure 10

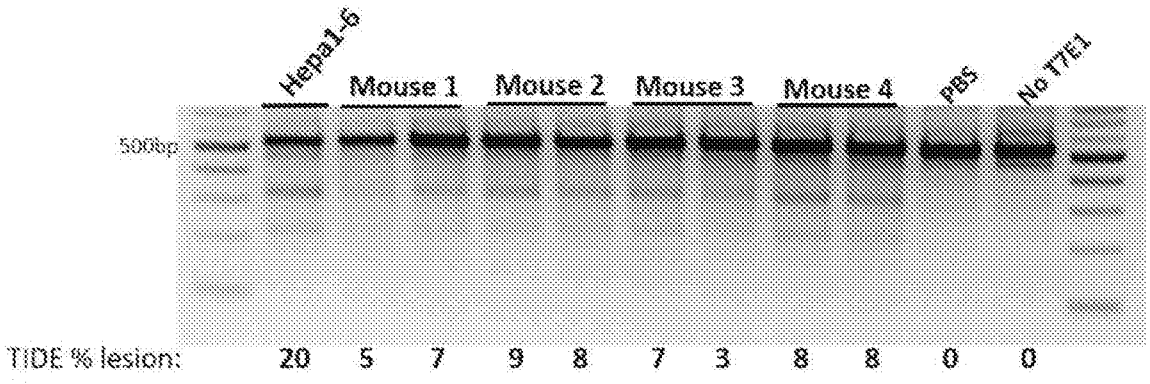
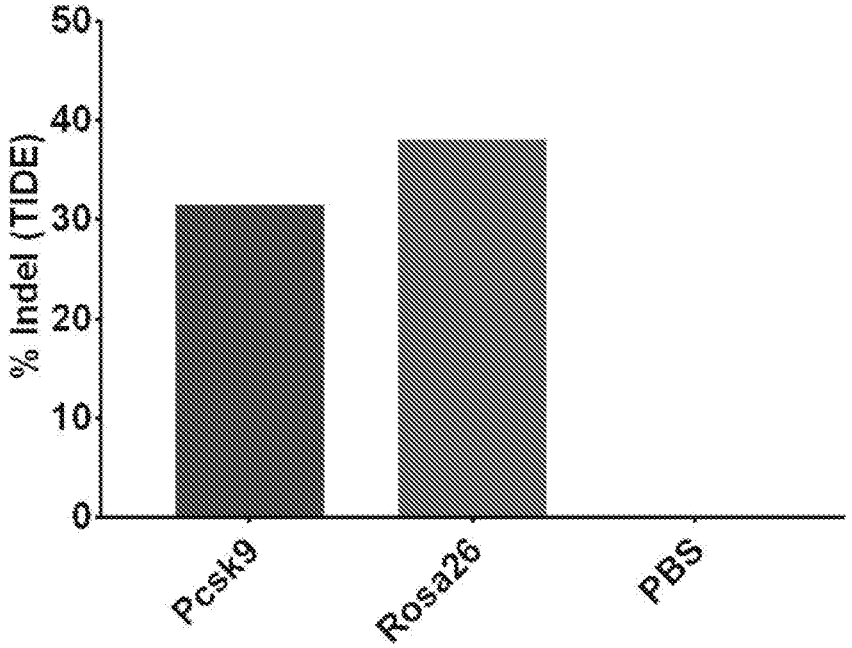

Hepa1-6
Mouse 1
Mouse 2
Mouse 3
Mouse 4
PBS
No T7E1
500bp
TIDE % lesion:
20 5 7 9 8 7 3 8 8 0 0

Figure 11

A


% Indel (TIDE)
50
40
30
20
10
0
Pcsk9
Rosa26
PBS

B

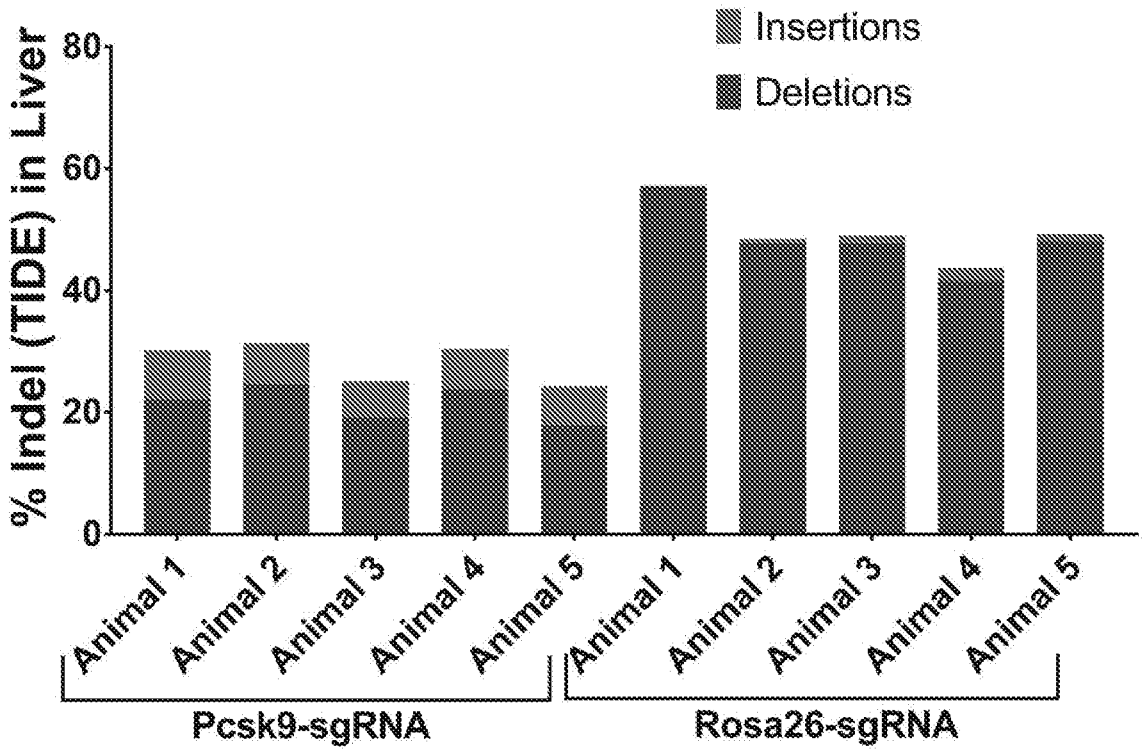

% Indel (TIDE) in Liver
80
60
40
20
0
Insertions
Deletions
Animal 1
Animal 2
Animal 3
Animal 4
Animal 5
Animal 1
Animal 2
Animal 3
Animal 4
Animal 5
Pcsk9-sgRNA
Rosa26-sgRNA

Figure 12

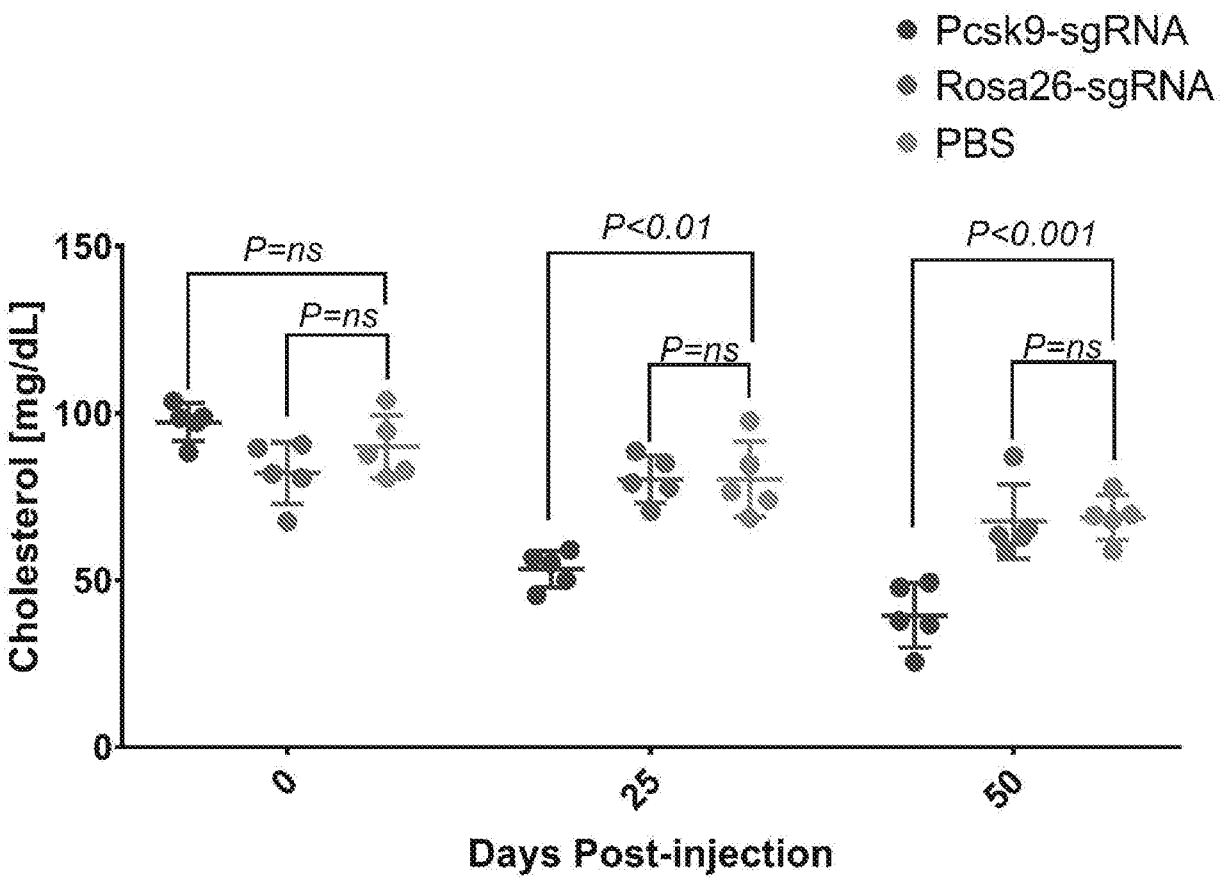
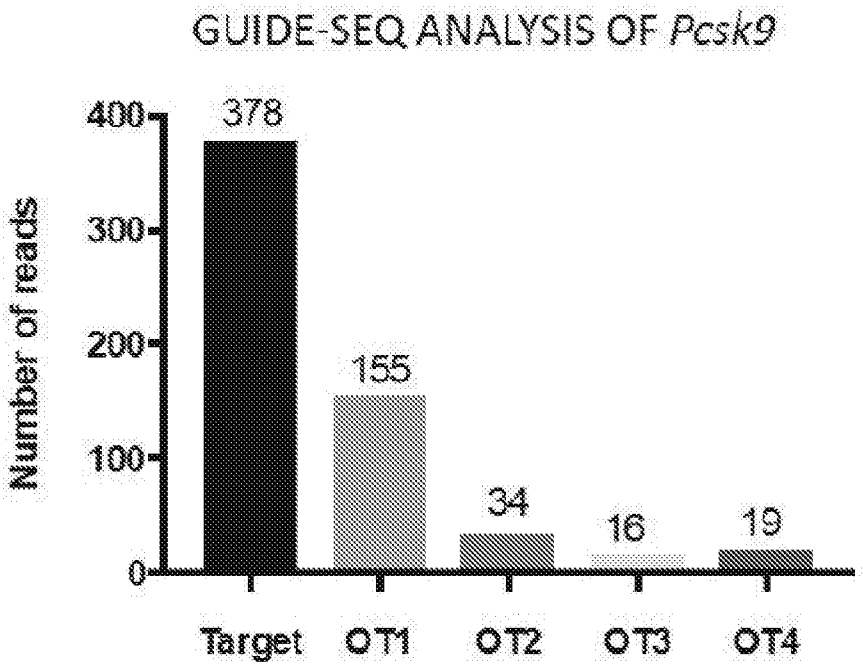

Pcsk9-sgRNA
Rosa26-sgRNA
PBS
Cholesterol [mg/dL]
150
100
50
0
P=ns
P=ns
P<0.01
P=ns
P<0.001
P=ns
0
25
50
Days Post-injection

Figure 13

A


GUIDE-SEQ ANALYSIS OF Pcsk9
Number of reads
400
300
200
100
0
378
155
34
16
19
Target
OT1
OT2
OT3
OT4

B

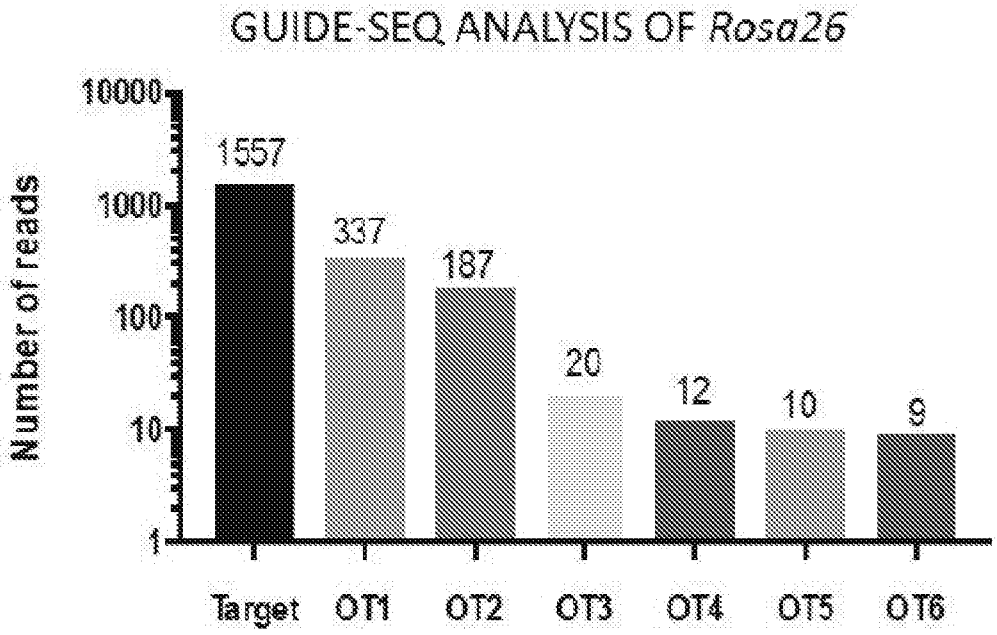

GUIDE-SEQ ANALYSIS OF Rosa26
Number of reads
10000
1000
100
10
1
1557
337
187
20
12
10
9
Target
OT1
OT2
OT3
OT4
OT5
OT6

Figure 14

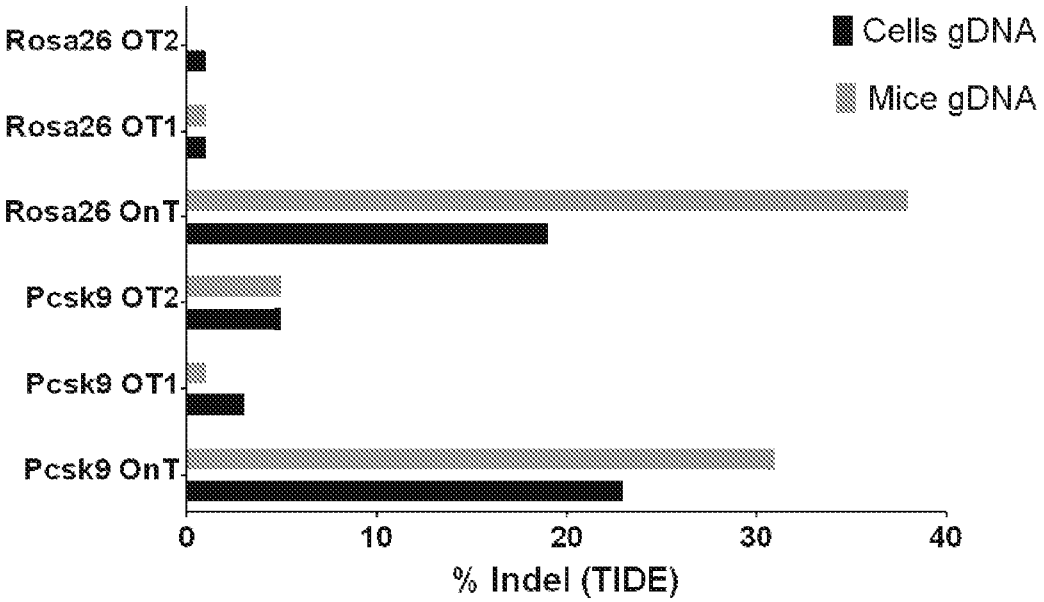

Rosa26 OT2
Rosa26 OT1
Rosa26 OnT
Pcsk9 OT2
Pcsk9 OT1
Pcsk9 OnT
Cells gDNA
Mice gDNA
0
10
20
30
40
% Indel (TIDE)

Figure 15

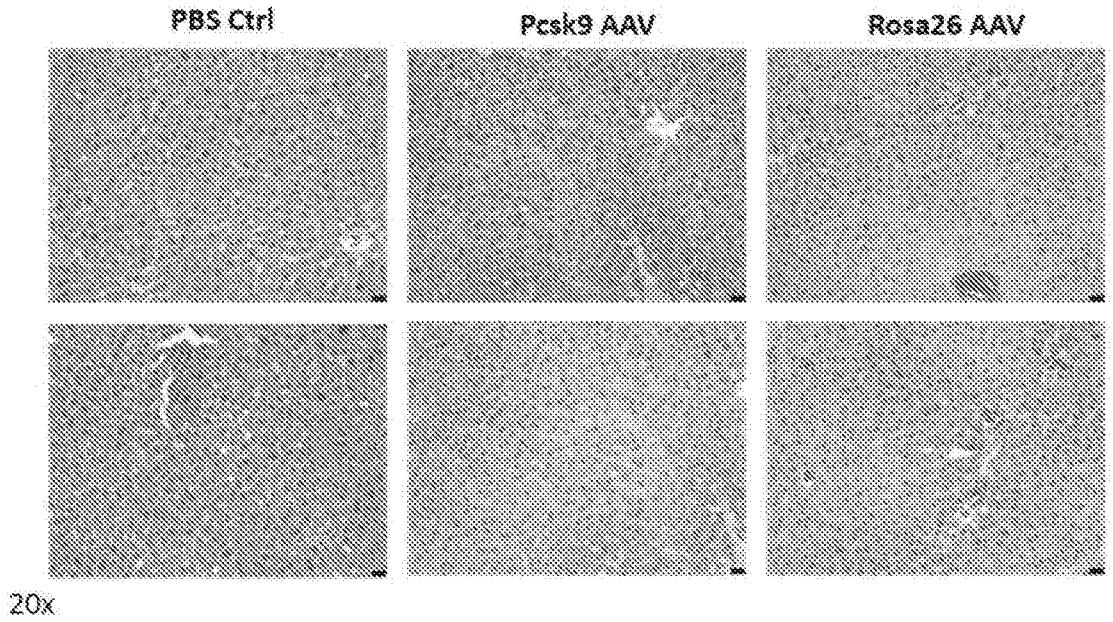


Figure 16

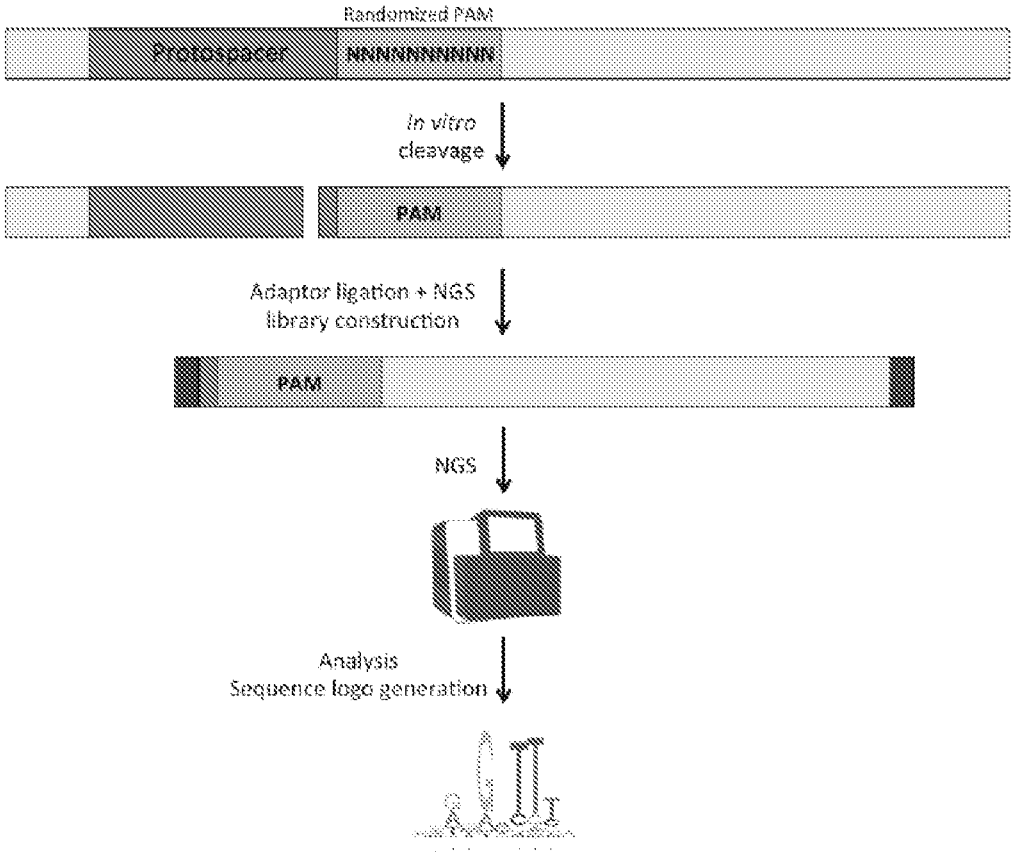

Randomized PAM
Protospacer
NNNNNNNNNN
In vitro cleavage
PAM
Adaptor ligation + NGS library construction
PAM
NGS
Analysis
Sequence logo generation

Figure 17

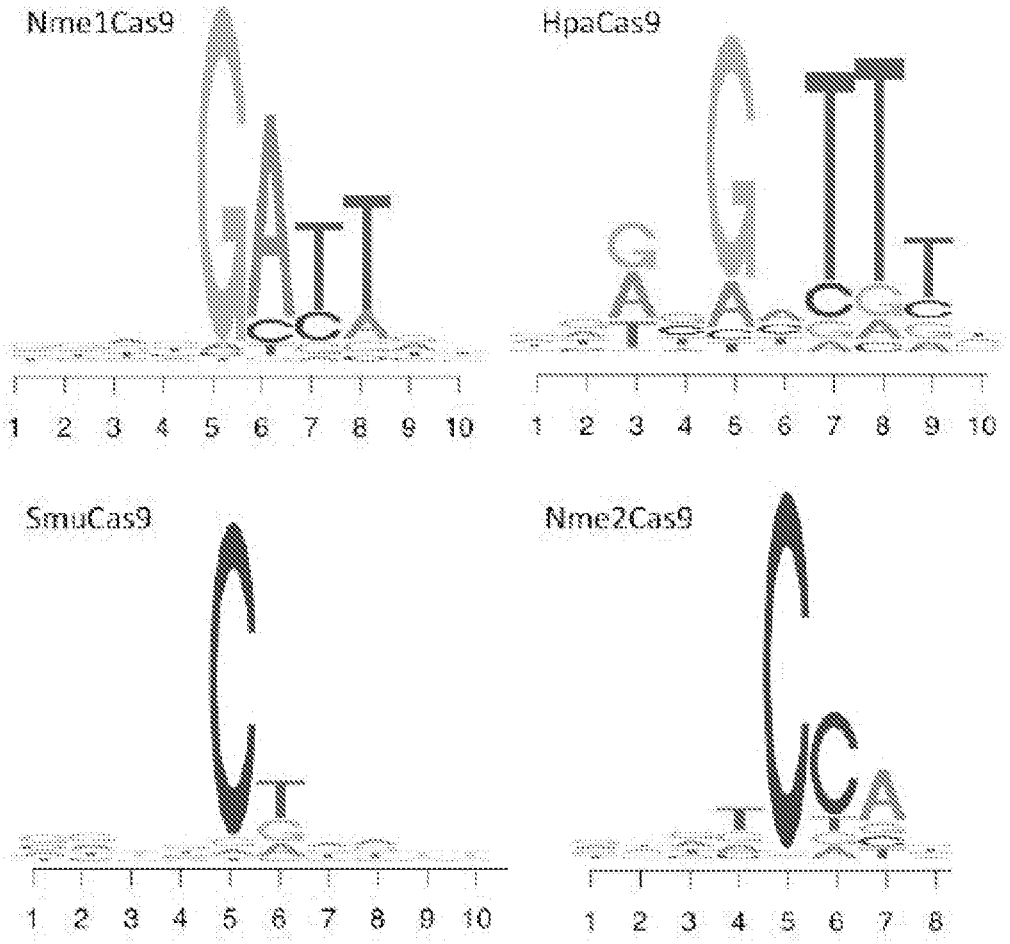

Nme1Cas9
1 2 3 4 5 6 7 8 9 10
HpaCas9
1 2 3 4 5 6 7 8 9 10
SmuCas9
1 2 3 4 5 6 7 8 9 10
Nme2Cas9
1 2 3 4 5 6 7 8

Figure 18

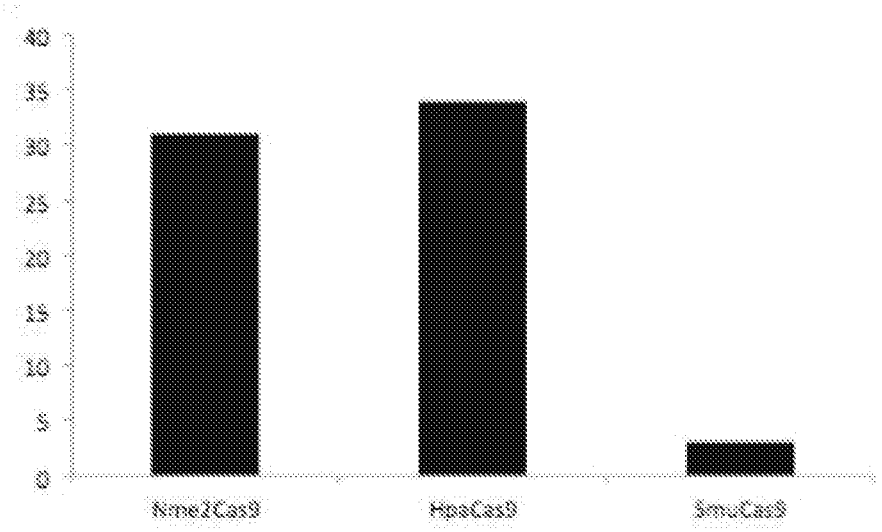


Figure 19

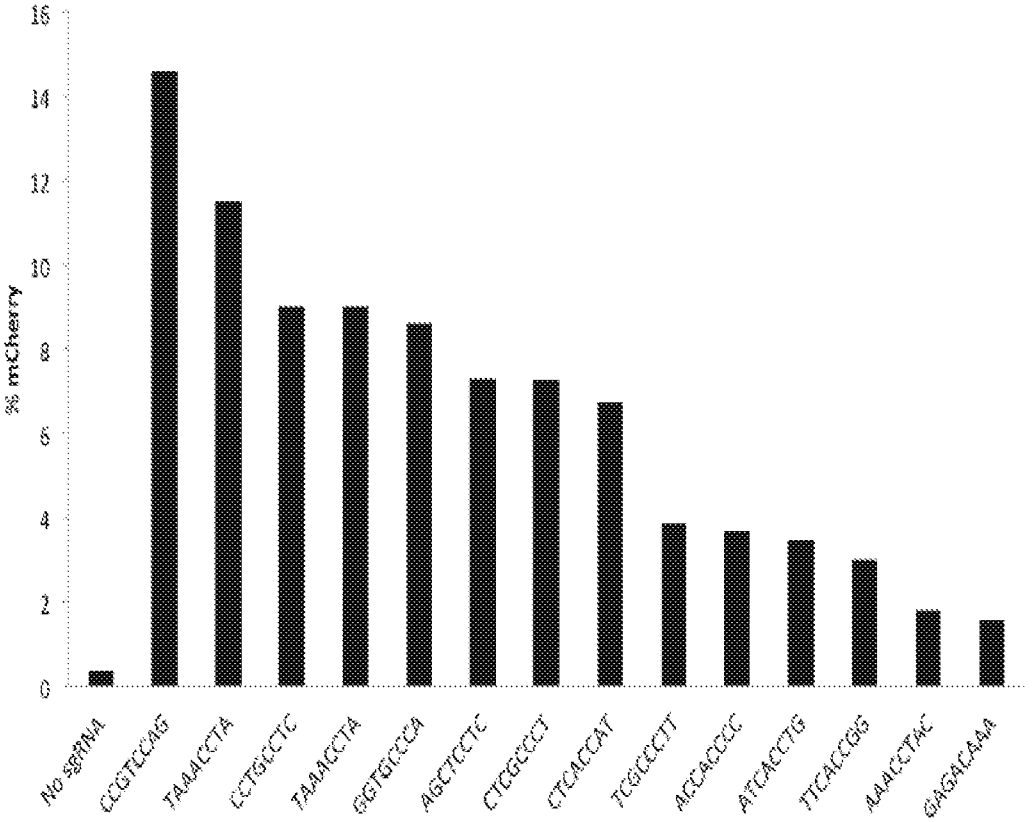

% mCherry
16
14
12
10
8
6
4
2
0
No sgRNA
CCGTCCAG
TAAACCTA
CCTGCCTC
TAAACCTA
GGTGCCCA
AGCTCCTC
CTCGCCCT
CTCACCAT
TCGCCCTT
ACCACCCC
ATCACCTG
TTCACCGG
AAACCTAC
GAGACAAA

Figure 20

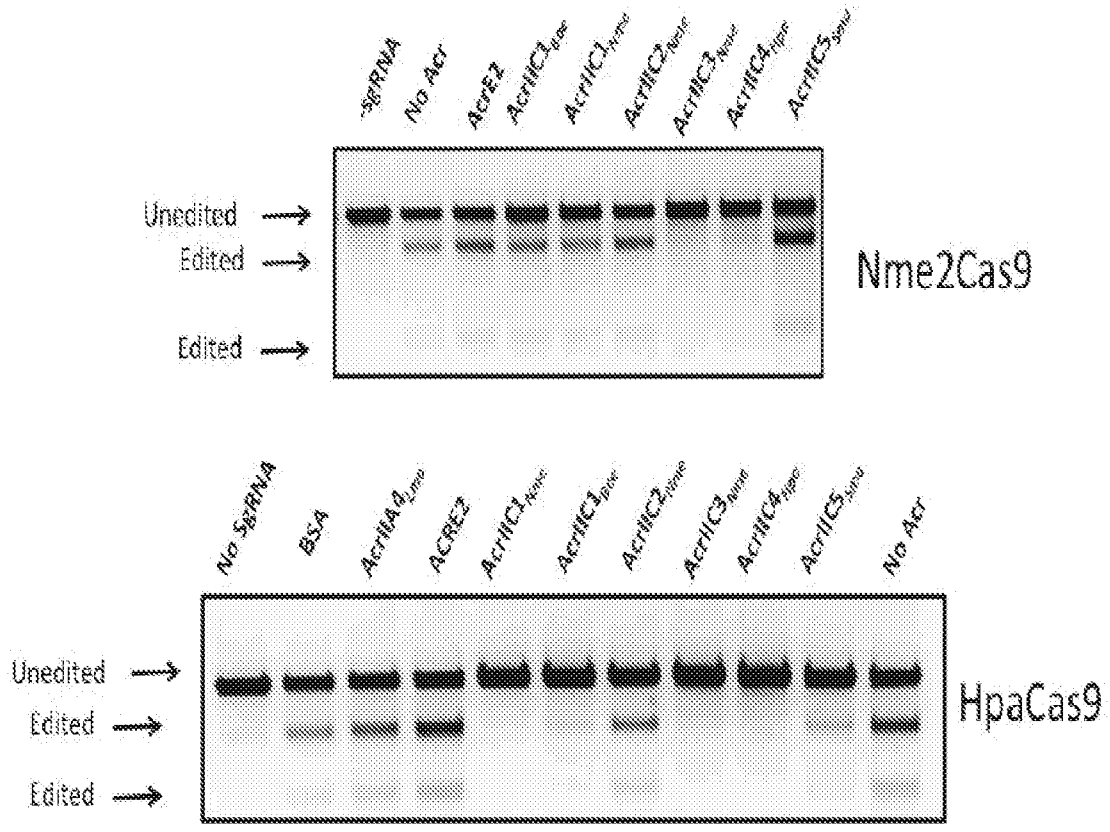

-sgRNA
No Acr
AcrIIC1
AcrIIC3
AcrIIC2
AcrIIC3
AcrIIC4
AcrIIC5
Unedited
Edited
Edited
Nme2Cas9
No SgRNA
BSA
AcrIIA4
ACRE2
AcrIIC1
AcrIIC3
AcrIIC2
AcrIIC3
AcrIIC4
AcrIIC5
No Acr
Unedited
Edited
Edited
HpaCas9

Figure 21

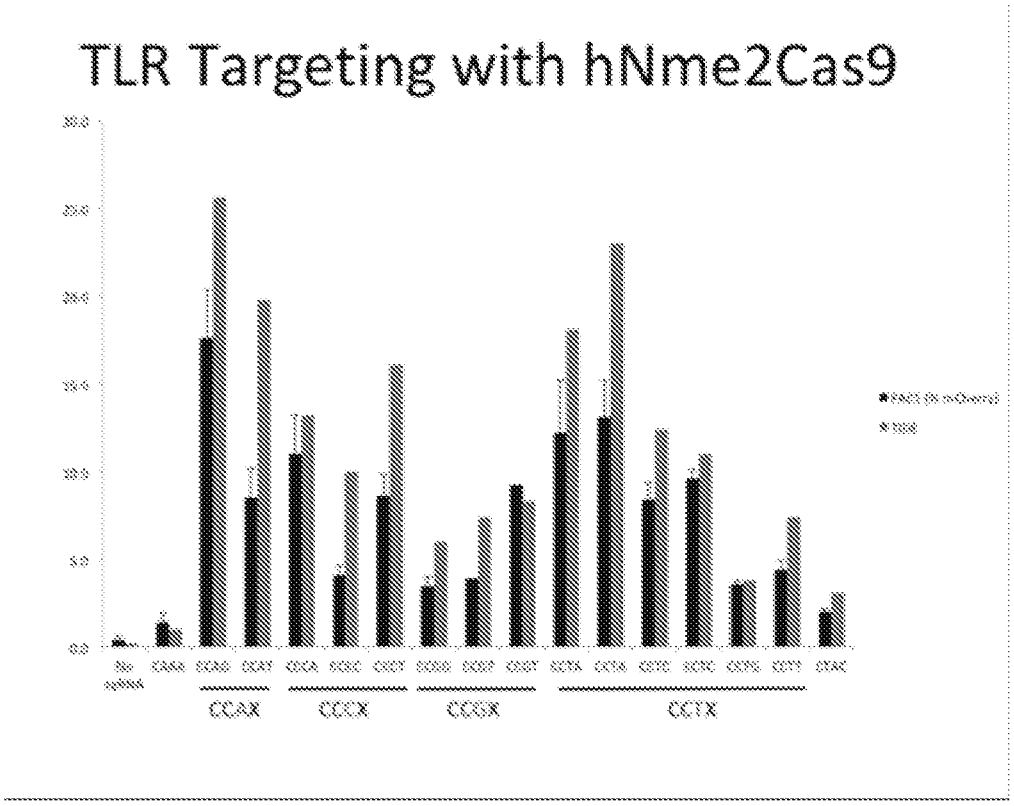


Figure 22

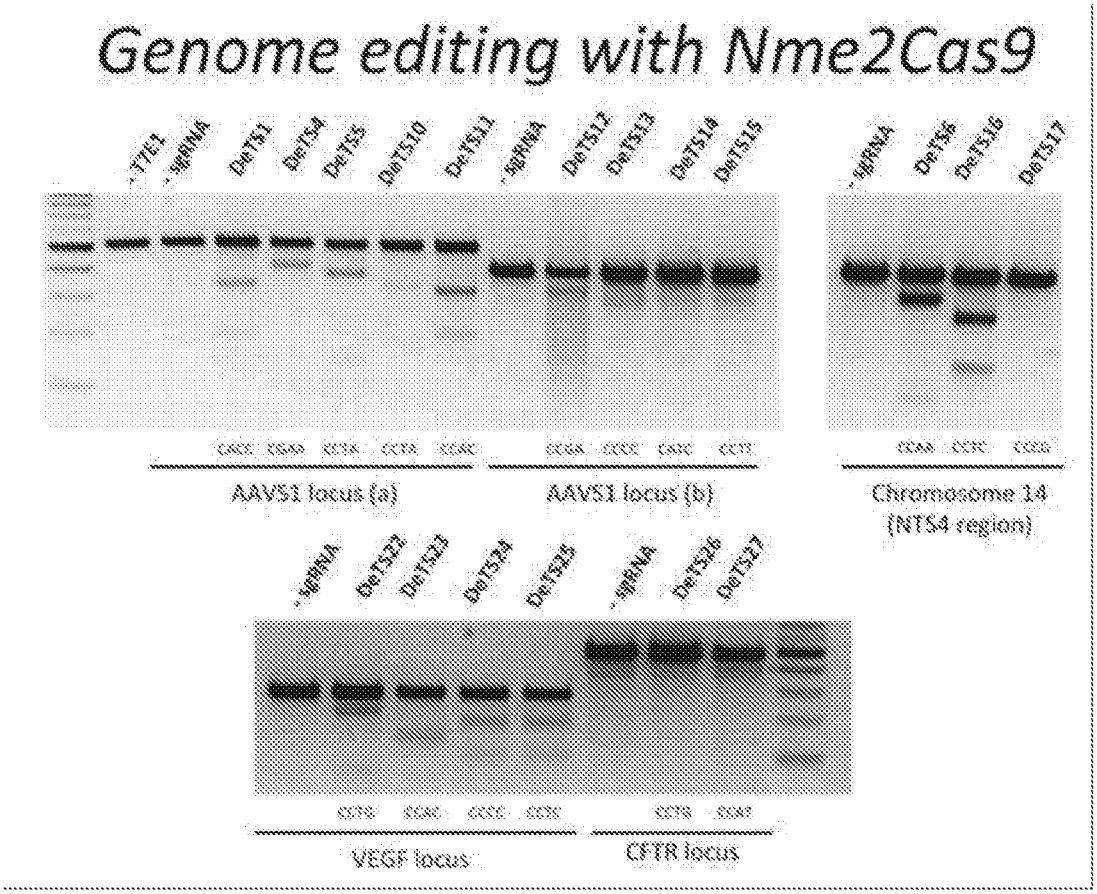

Genome editing with Nme2Cas9
- T7E1
- sgRNA
DeTS1
DeTS4
DeTS5
DeTS10
DeTS11
- sgRNA
DeTS12
DeTS13
DeTS14
DeTS15
- sgRNA
DeTS16
DeTS16
DeTS17
AAVS1 locus (a)
AAVS1 locus (b)
Chromosome 14
(NTS4 region)
- sgRNA
DeTS22
DeTS23
DeTS24
DeTS25
- sgRNA
DeTS26
DeTS27
VEGF locus
CFTR locus

Figure 23

ATGGCTGCCTTCAAACCTAATCCAATCAACTACATCCTCGGCCTCGATATCGGCATCGCATCCGTCGGC
TGGGCGATGGTAGAAATTGACGAAGAAGAAAACCCCATCCGCCTGATTGATTTGGGCGTGCGCGTATT
TGAGCGTGCCGAAGTACCGAAAACAGGCGACTCCCTTGCCATGGCAAGGCGTTTGGCGCGCAGTGTCC
GCCGCCTGACCCGCCGTCGCGCCCATCGCCTGCTTCGGGCCCGCCGCCTATTGAAACGCGAAGGCGTA
TTACAAGCCGCTGATTTTGACGAAAACGGCTTGATCAAATCCTTACCGAATACACCATGGCAACTTCG
CGCAGCCGCATTAGACCGCAAACTGACGCCTTTAGAGTGGTCGGCAGTCTTGTTGCATTTAATCAAAC
ACCGCGGTTATTTGTCGCAAAGAAAAAACGAGGGCGAAACTGCCGATAAAGAGCTTGGCGCTTTGCTT
AAAGGCGTGGCCAACAATGCCCATGCCTTACAGACAGGCGATTTCCGCACACCGGCCGAATTGGCTTT
AAATAAATTTGAGAAAGAAAGCGGCCATATCCGCAATCAGCGCGGCGATTATTCGCATACGTTCAGCC
GCAAAGATTTACAGGCGGAGCTGATTTTGCTGTTTGAAAAACAAAAAGAATTTGGCAATCCGCATGTT
TCAGGCGGCCTTAAAGAAGGTATTGAAACCCTACTGATGACGCAACGCCCTGCCCTGTCCGGCGATGC
CGTTCAAAAAATGTTGGGGCATTGCACCTTCGAACCGGCAGAGCCGAAAGCCGCTAAAAACACCTAC
ACAGCCGAACGTTTCATCTGGCTGACCAAGCTGAACAACCTGCGTATTTTAGAGCAAGGCAGCGAGCG
GCCATTGACCGATACCGAACGCGCCACGCTTATGGACGAGCCATACAGAAAATCCAAACTGACTTACG
CACAAGCCCGTAAGCTGCTGGGTTTAGAAGATACCGCCTTTTTCAAAGGCTTGCGCTATGGTAAAG
ACAATGCCGAAGCCTCAACATTGATGGAAATGAAGGCCTACCATGCCATCAGCCGTGCACTGGAAAA
AGAAGGATTGAAAGATAAAAAATCCCCATTAAACCTTTCTTCCGAATTACAAGATGAAATCGGCACGG
CATTCTCCCTGTTCAAAACCGATGAAGACATTACAGGCCGTCTGAAAGACCGTGTTCAGCCCGAAATC
TTAGAAGCGCTGTTGAAACACATCAGCTTCGATAAGTTCGTCCAAATTTCCTTGAAAGCATTGCGCCG
AATTGTGCCTCTAATGGAGCAAGGCAAACGTTACGATGAAGCCTGCGCCGAAATCTACGGAGACCATT
ACGGCAAGAAAAATACGGAAGAAAAAATTTATCTGCCGCCCATCCCTGCCGACGAGATCCGCAACCC
CGTCGTCTTGCGCGCCTTATCTCAAGCACGTAAGGTCATTAACGGCGTGGTACGCCGTTACGGCTCCCC
AGCTCGTATCCATATTGAAACGGCAAGGGAAGTAGGTAAATCGTTTAAAGACCGCAAAGAAATCGAA
AAACGCCAAGAAGAAAACCGCAAAGACCGGGAAAAAGCCGCCGCCAAATTCCGAGAGTATTTCCCCA
ATTTTGTCGGCGAACCCAAATCAAAAGATATTCTGAAACTGCGCCTGTACGAGCAACAACACGGCAAA
TGCCTGTATTCGGGCAAAGAAATCAACTTAGTCCGTCTGAACGAAAAAGGCTATGTCGAAATCGACCA
TGCCCTGCCGTTTTCGCGCACATGGGACGACAGTTTCAACAATAAAGTGCTGGTATTGGGCAGCGAAA
ACCAAAACAAAGGCAATCAAACCCCTTACGAATACTTCAACGGCAAAGACAACAGCCGCGAATGGCA
GGAATTTAAAGCGCGTGTCGAAACCAGCCGTTTCCCGCGCAGTAAAAAACAACGGATTCTGCTGCAAA
AATTCGATGAAGACGGCTTTAAAGAATGCAATCTGAACGACACGCGCTACGTCAACCGTTTCCTGTGC
CAATTTGTTGCCGACCATATATTGCTGACAGGTAAAGGGAAAAGACGTGTCTTTGCCTCAAACGGACA
AATTACCAATCTGTTGCGCGGCTTTTGGGGATTGCGCAAAGTGCGTGCGGAAAACGACCGCCATCACG
CCTTGGACGCTGTAGTCGTTGCCTGCTCGACCGTTGCCATGCAGCAGAAAATTACCCGTTTTGTACGCT
ATAAAGAGATGAACGCGTTTGACGGTAAAACCATAGACAAAGAAACAGGAAAAGTGCTGCATCAAAA
AACACACTTCCCACAACCTTGGGAATTTTTCGCACAAGAAGTCATGATTCGCGTCTTCGGCAAACCGG
ACGGCAAACCCGAATTCGAAGAAGCCGATACCCCAGAAAAACTGCGCACGTTGCTTGCCGAAAAATT
ATCATCTCGCCCCGAAGCCGTACACGAATACGTTACGCCACTGTTTGTTTCACGCGCGCCCAATCGGA
AGATGAGCGGTGCACATAAAGATACTTTGAGATCTGCTAAACGATTTGTTAAACATAATGAAAAAATT
AGTGTTAAACGAGTATGGTTAACCGAAATCAAGTTGGCCGACCTTGAAAATATGGTTAATTATAAAAA
TGGTAGAGAGATTGAATTATATGAGGCTCTTAAGGCGCGTTTAGAGGCATATGGAGGTAATGCTAAAC
AAGCATTTGACCCTAAGGACAATCCGTTTTATAAAAAGGGAGGACAACTGGTTAAAG
CTGTGAGGGTCGAAAAAACCCAAGAGAGCGGAGTCTTATTAAATAAAAAAAATGCTTATACCATTGC
AGATAATGGAGACATGGTACGTGTTGATGTGTTCTGTAAAGTAGATAAGAAAGGAAAAAATCAGTATT
TTATTGTTCCCATCTATGCTTGGCAGGTTGCTGAAAACATTCTTCCCGATATTGATTGTAAGGGATACC
GGATTGATGATAGCTATACATTCTGTTTTAGCTTGCATAAGTATGATCTGATTGCTTTTCAAAAAGATG
AAAAATCTAAAGTAGAATTCGCCTACTATATCAACTGTGATAGCTCTAATGGACGATTCTATTTAGCTT
GGCATGATAAAGGCTCTAAAGAACAGCAATTCCGTATTAGCACCCAAAATCTTGTATTGATACAAAAA
TACCAAGTTAACGAACTGGGCAAAGAAATCAGACCATGCCGTCTGAAAAAACGC
CCACCTGTCCGTTAA

Figure 24

MAAFKPNPINYILGLDIGIASVGWAMVEIDEEENPIRLIDLGVRVFERAEVPKTGDSLAM
ARRLARSVRRLTRRRAHRLLRARRLLKREGVLQAADFDENGLIKSLPNTPWQLRAAAL
DRKLTPLEWSAVLLHLIKHRGYLSQRKNEGETADKELGALLKGVANNAHALQTGDFRT
PAELALNKFEKESGHIRNQRGDYSHTFSRKDLQAELILLFEKQKEFGNPHVSGGLKEGIE
TLLMTQRPALSGDAVQKMLGHCTFEPAEPKAAKNTYTAERFIWLTKLNNLRILEQGSER
PLTDTERATLMDEPYRKSKLTYAQARKLLGLEDTAFFKGLRYGKDNAEASTLMEMKA
YHAISRALEKEGLKDKKSPLNLSSELQDEIGTAFSLFKTDEDITGRLKDRVQPEILEALLK
HISFDKFVQISLKALRRIVPLMEQGKRYDEACAEIYGDHYGKKNTEEKIYLPPIPADEIRN
PVVLRALSQARKVINGVVRRYGSPARIHIETAREVGKSFKDRKEIEKRQEENRKDREKA
AAKFREYFPNFVGEPKSKDILKLRLYEQQHGKCLYSGKEINLVRLNEKGYVEIDHALPFS
RTWDDSFNNKVLVLGSENQNKGNQTPYEYFNGKDNSREWQEFKARVETSRFPRSKKQ
RILLQKFDEDGFKECNLNDTRYVNRFLCQFVADHILLTGKGKRRVFASNGQITNLLRGF
WGLRKVRAENDRHHALDAVVVACSTVAMQQKITRFVRYKEMNAFDGKTIDKETGKVL
HQKTHFPQPWEFFAQEVMIRVFGKPDGKPEFEEADTPEKLRTLLAEKLSSRPEAVHEYV
TPLFVSRAPNRKMSGAHKDTLRSAKRFVKHNEKISVKRVWLTEIKLADLENMVNYKNG
REIELYEALKARLEAYGGNAKQAFDPKDNPFYKKGGQLVKAVRVEKTQESGVLLNKK
NAYTIADNGDMVRVDVFCKVDKKGKNQYFIVPIYAWQVAENILPDIDCKGYRIDDSYTF
CFSLHKYDLIAFQKDEKSKVEFAYYINCDSSNGRFYLAWHDKGSKEQQFRISTQNLVLIQ
KYQVNELGKEIRPCRLKKRPPVR

Figure 25

ATGGCCGCCTTCAAGCCTAACCCAATCAATTACATCCTGGGACTGGACATCGGAATCGCATCCGTGGGATGGGCTATGGTGGAGATCGACGA
GGAGGAGAATCCTATCCGGCTGATCGATCTGGGCGTGAGAGTGTTTGAGAGGGCCGAGGTGCCAAAGACCGGCGATTCTCTGGCTATGGCCC
GGAGACTGGCACGGAGCGTGAGGCGCCTGACACGGAGAAGGGCACACAGGCTGCTGAGGGCACGCCGGCTGCTGAAGAGAGAGGGCGTGCT
GCAGGCAGCAGACTTCGATGAGAATGGCCTGATCAAGAGCCTGCCAAACACCCCCTGGCAGCTGAGAGCAGCCGCCCTGGACAGGAAGCTG
ACACCACTGGAGTGGTCTGCCGTGCTGCTGCACCTGATCAAGCACCGCGGCTACCTGAGCCAGCGGAAGAACGAGGGAGAGACAGCAGACA
AGGAGCTGGGCGCCCTGCTGAAGGGAGTGGCCAACAATGCCCACGCCCTGCAGACCGGCGATTTCAGGACACCTGCCGAGCTGGCCCTGAAT
AAGTTTGAGAAGGAGTCCGGCCACATCAGAAACCAGAGGGGCGACTATAGCCACACCTTCTCCCGCAAGGATCTGCAGGCCGAGCTGATCCT
GCTGTTCGAGAAGCAGAAGGAGTTTGGCAATCCACACGTGAGCGGAGGCCTGAAGGAGGGAATCGAGACCCTGCTGATGACACAGAGGCCT
GCCCTGTCCGGCGACGCAGTGCAGAAGATGCTGGGACACTGCACCTTCGAGCCTGCAGAGCCAAAGGCCGCCAAGAACACCTACACAGCCGA
GCGGTTTATCTGGCTGACAAAGCTGAACAATCTGAGAATCCTGGAGCAGGGATCCGAGAGGCCACTGACCGACACAGAGAGGGCCACCCTGA
TGGATGAGCCTTACCGGAAGTCTAAGCTGACATATGCCCAGGCCAGAAAGCTGCTGGGCCTGGAGGACACCGCCTTCTTTAAGGGCCTGAGA
TACGGCAAGGATAATGCCGAGGCCTCCACACTGATGGAGATGAAGGCCTATCACGCCATCTCTCGCGCCCTGGAGAAGGAGGGCCTGAAGGA
CAAGAAGTCCCCCCTGAACCTGAGCTCCGAGCTGCAGGATGAGATCGGCACCGCCTTCTCTCTGTTTAAGACCGACGAGGATATCACAGGCC
GCCTGAAGGACAGGGTGCAGCCTGAGATCCTGGAGGCCCTGCTGAAGCACATCTCTTTCGATAAGTTTGTGCAGATCAGCCTGAAGGCCCTG
AGAAGGATCGTGCCACTGATGGAGCAGGGCAAGCGGTACGACGAGGCCTGCGCCGAGATCTACGGCGATCACTATGGCAAGAAGAACACAG
AGGAGAAGATCTATCTGCCCCCTATCCCTGCCGACGAGATCAGAAATCCTGTGGTGCTGAGGGCCCTGTCCCAGGCAAGAAAAGTGATCAAC
GGAGTGGTGCGCCGGTACGGATCTCCAGCCCGGATCCACATCGAGACCGCCAGAGAAGTGGGCAAGAGCTTCAAGGACCGGAAGGAGATCG
AGAAGAGACAGGAGGAGAATCGCAAGGATCGGGAGAAGGCTGCCGCCAAGTTTAGGGAGTACTTCCCTAACTTTGTGGGCGAGCCAAAGTC
TAAGGACATCCTGAAGCTGCGCCTGTACGAGCAGCAGCACGGCAAGTGTCTGTATAGCGGCAAGGAGATCAATCTGGTGCGGCTGAACGAGA
AGGGCTATGTGGAGATCGATCACGCCCTGCCTTTCTCCAGAACCTGGGACGATTCTTTTAACAATAAGGTGCTGGTGCTGGGCAGCGAGAACC
AGAATAAGGGCAATCAGACACCATACGAGTATTTCAATGGCAAGGACAACTCCAGGGAGTGGCAGGAGTTCAAGGCCCGCGTGGAGACCTC
TAGATTTCCCAGGAGCAAGAAGCAGCGGATCCTGCTGCAGAAGTTCGACGAGGATGGCTTTAAGGAGTGCAACCTGAATGACACCAGATACG
TGAACCGGTTCCTGTGCCAGTTTGTGGCCGATCACATCCTGCTGACCGGCAAGGGCAAGAGAAGGGTGTTCGCCTCTAATGGCCAGATCACAA
ACCTGCTGAGGGGATTTTGGGGACTGAGGAAGGTGCGGGCAGAGAATGACAGACACCACGCACTGGATGCAGTGGTGGTGGCATGCAGCAC
CGTGGCAATGCAGCAGAAGATCACAAGATTCGTGAGGTATAAGGAGATGAACGCCTTTGACGGCAAGACCATCGATAAGGAGACAGGCAAG
GTGCTGCACCAGAAGACCCACTTCCCCCAGCCTTGGGAGTTCTTTGCCCAGGAAGTGATGATCCGGGTGTTCGGCAAGCCAGACGGCAAGCCT
GAGTTTGAGGAGGCCGATACCCCAGAGAAGCTGAGGACACTGCTGGCAGAGAAGCTGTCTAGCAGGCCAGAGGCAGTGCACGAGTACGTGA
CCCCACTGTTCGTGTCCAGGGCACCCAATCGGAAGATGTCTGGCGCCCACAAGGACACACTGAGAAGCGCCAAGAGGTTTGTGAAGCACAAC
GAGAAGATCTCCGTGAAGAGAGTGTGGCTGACCGAGATCAAGCTGGCCGATCTGGAGAACATGGTGAATTACAAGAACGGCAGGGAGATCG
AGCTGTATGAGGCCCTGAAGGCAAGGCTGGAGGCCTACGGAGGAAATGCCAAGCAGGCCTTCGACCCAAAGGATAACCCCTTTTATAAGAAG
GGAGGACAGCTGGTGAAGGCCGTGCGGGTGGAGAAGACCCAGGAGAGCGGCGTGCTGCTGAATAAGAAGAACGCCTACACAATCGCCGACA
ATGGCGATATGGTGAGAGTGGACGTGTTCTGTAAGGTGGATAAGAAGGGCAAGAATCAGTACTTTATCGTGCCTATCTATGCCTGGCAGGTG
GCCGAGAACATCCTGCCAGACATCGATTGCAAGGGCTACAGAATCGACGATAGCTATACATTCTGTTTTTCCCTGCACAAGTATGACCTGATC
GCCTTCCAGAAGGATGAGAAGTCCAAGGTGGAGTTTGCCTACTATATCAATTGCGACTCCTCTAACGGCAGGTTCTACCTGGCCTGGCACGAT
AAGGGCAGCAAGGAGCAGCAGTTTCGCATCTCCACCCAGAATCTGGTGCTGATCCAGAAGTATCAGGTGAACGAGCTGGGCAAGGAGATCA
GGCCATGTCGGCTGAAGAAGCGCCCACCCGTGCGGGGCACCGGCGGGCCCAAGAAGAAGAGGAAGGTATACCCATACGATGTTCCGGACTAT
GCGGCTATCCTATGACGTCCCGGACTATGCAGGATCCTATCCTTATGACGTTCCAGATTACGCTGGATCCGCCGCTCCGGCAGCTAAGAAA
AAGAAACTGGATTTCGAATCCGGATAA

MAAFKPNPINYILGLDIGIASVGWAMVEIDEEENPIRLIDLGVRVFERAEVPKTGDSLAMARRLARSVRRLTRRRAHRLLRARRLLKREGVLQAADF
DENGLIKSLPNTPWQLRAAALDRKLTPLEWSAVLLHLIKHRGYLSQRKNEGETADKELGALLKGVANNAHALQTGDFRTPAELALNKFEKESGHIR
NQRGDYSHTFSRKDLQAELILLFEKQKEFGNPHVSGGLKEGIETLLMTQRPALSGDAVQKMLGHCTFEPAEPKAAKNTYTAERFIWLTKLNNLRILE
QGSERPLTDTERATLMDEPYRKSKLTYAQARKLLGLEDTAFFKGLRYGKDNAEASTLMEMKAYHAISRALEKEGLKDKKSPLNLSSELQDEIGTAF
SLFKTDEDITGRLKDRVQPEILEALLKHISFDKFVQISLKALRRIVPLMEQGKRYDEACAEIYGDHYGKKNTEEKIYLPPIPADEIRNPVVLRALSQAR
KVINGVVRRYGSPARIHIETAREVGKSFKDRKEIEKRQEENRKDREKAAAKFREYFPNFVGEPKSKDILKLRLYEQQHGKCLYSGKEINLVRLNEKG
YVEIDHALPFSRTWDDSFNNKVLVLGSENQNKGNQTPYEYFNGKDNSREWQEFKARVETSRFPRSKKQRILLQKFDEDGFKECNLNDTRYVNRFLC
QFVADHILLTGKGKRRVFASNGQITNLLRGFWGLRKVRAENDRHHALDAVVVACSTVAMQQKITRFVRYKEMNAFDGKTIDKETGKVLHQKTHF
PQPWEFFAQEVMIRVFGKPDGKPEFEEADTPEKLRTLLAEKLSSRPEAVHEYVTPLFVSRAPNRKMSGAHKDTLRSAKRFVKHNEKISVKRVWLTEI
KLADLENMVNYKNGREIELYEALKARLEAYGGNAKQAFDPKDNPFYKKGGQLVKAVRVEKTQESGVLLNKKNAYTIADNGDMVRVDVFCKVDK
KGKNQYFIVPIYAWQVAENILPDIDCKGYRIDDSYTFCFSLHKYDLIAFQKDEKSKVEFAYYINCDSSNGRFYLAWHDKGSKEQQFRISTQNLVLIQK
YQVNELGKEIRPCRLKKRPPVRGTGGPKKKRKV[redacted]GSAAPAAKKSKLDFESG*

Figure 27

MENKNLNYILGLDLGIASVGWAVVEIDEKENPLRLIDVGVRTFERAEVPKTGESLALSRR
LARSARRLTQRRVARLKKAKRLLKSENILLSTDERLPHQVWQLRVEGLDHKLERQEWA
AVLLHLIKHRGYLSQRKNESKSENKELGALLSGVDNNHKLLQQATYRSPAELAVKKFE
VEEGHIRNQQGAYTHTFSRLDLLAEMELLFSRQQHFGNPFASEKLLENLTALLMWQKPA
LSGEAILKMLGKCTFEDEYKAAKNTYSAERFVWITKLNNLRIQENGLERALNDNERLAL
MEQPYDKNRLFYSQVRSILKLSDEAIFKGLRYSGEDKKAIETKAVLMEMKAYHQIRKVL
EGNNLKAEWAELKANPTLLDEIGTAFSLYKTDEDISAYLAGKLSQPVLNALLENLSFDK
FIQLSLKALYKLLPLMQQGLRYDEACREIYGDHYGKKTEENHHFLPQIPADEIRNPVVLR
TLTQARKVINGVVRLYGSPARIHIETGREVGKSYKDRRELEKRQEENRKQRENAIKEFKE
YFPHFAGEPKAKDILKMRLYKQQNAKCLYSGKPIELHRLLEKGYVEVDHALPFSRTWD
DSFNNKVLVLANENQNKGNLTPFEWLDGKHNSERWRAFKALVETSAFPYAKKQRILSQ
KLDEKGFIERNLNDTRYVARFLCNFIADNMHLTGEGKRKVFASNGQITALLRSRWGLAK
SREDNDRHHALDAVVVACSTVAMQQKITRFVRFEAGDVFTGERIDRETGEIIPLHFPTPW
QFFKQEVEIRIFSDNPKLELENRLPDRPQANHEFVQPLFVSRMPTRKMTGQGHMETVKS
AKRLNEGISVIKMPLTKLKLKDLELMVNREREKDLYDTLKARLEAFNDDPAKAFAEPFI
KKGGAIVKSVRVEQIQKSGVLVREGNGVADNASMVRVDVFTKGGKYFLVPIYTWQVA
KGILPNKAATQYKDEEDWEVMDNSATFKFSLHPNDLVKLVTKKKTILGYFNGLNRATG
NIDIKEHDLDKSKGKQGIFEGVGIKLALSFEKYQVDELGKNIRLCKPSKRQPVR*

Figure 28

ATGGAAAAATTTCACTATGTATTGGGTTTGGATTTGGGTATCGCCTCTGTGGGGTGGGCTGCCATTGAA
ATTGACAAGGAAACCGAAACATCAATCGGTTTATTGGATTGCGGTGTCAGAACATTTGAACGTGCAGA
AGTACCCAAAACAGGCGATTCTCTTGCCAAAGCTCGCCGTGAAGCCAGAAGTACTCGCCGTTTAATTC
GCAGACGTTCGCATCGCTTATTACGTTTAAAACGTTTATTGAAACGTGAAATTTTCAGGCAGCCTGAAA
CGTTTAAAGACTTACCAATCAATGCTTGGCAATTGCGTGTTAAAGGCTTGGATAGTCGGTTGAATGAA
TATGAATGGGCGGCCGTTTTATTGCATTTGGTGAAGCATCGCGGTTATTTATCGCAACGCAAAAGCGA
AATGAGCGAAACAGACAGCAAATCTGAAATGGGCAGATTACTGGCAGGTGTGGCGGAAAATCACCAA
CTTTTACAACAAGAACAATATCGTACACCAGCCGAATTAGCACTCAAAAAATTTGTGAAACATTTTCG
CAATAAAGGTGGCGATTATGCACACACTTTCAACCGTTTGGATTTGCAAGCCGAATTGCATTTATTGTT
TCAAAAACAACGTGAATTAGGCAATCCATTCACTTCACCAGAATTGGAACGGCAAGTTGATGATTTGT
TGATGACGCAGCGCAGTGCTTTACAAGGTGATGCGATTTTGAAAATGTTGGGTCATTGTGGGTTTGAA
CCTGAACAATTCAAAGCAGCGAAAAACACATTCAGTGCCGAACGTTTTATTTGGTTGACAAAACTCAA
TAATCTTCGCATTCAAGACCAAGGCAAAGAACGTGCGTTAACTGCCGATGAGCGTACCAAATTGTTGG
ACGAGCCTTATAAAAAAAGTAAATTGACTTACGCACAAGTTCGCAAATTATTAAGCTTGCCTCAAACT
GCTATTTTTAAAGGTTTGCGTTATGATTTGGAACATGACAAAAAAGCAGAAAACAGTACGTTGATGGA
AATGAAATCCTATCACAACATCCGCCAAACATTGGAAAAATCAGGTTTGAAAACAGAATGGCAAAGT
ATTGCCACGCAGCCTGAAATTTTAGATGCAATTGGCACGGCGTTTTCCATTTATAAAACCGATGAAGA
TATTTCGCATGAATTAAAAACGTGCAGGCTGCCTGAAAACGTATTGAATGAATTACTGAAAAACATCA
ATTTTGATGGATTCATTCAATTATCGTTGACTGCATTACGCAAAATTTTGCCCTTGATGGAACAAGGCT
ACCGTTATGATGAAGCGTGTACCCAAATTTACGGTAATCATCATTCAGGCAGCTTGCAACAAGAATCA
AAGCAATTTTTGCCACATATTCCGATTGATGATGTCCGAAATCCTGTGGTGTTCCGTACTTTGACCCAA
GCAAGAAAAGTGGTGAATGCGATTATTCGTCGGTATGGTTCGCCAGCTCGTGTGCATATTGAGATGGC
GCGTGAATTGGGTAAGTCTAAATCAGACCGTGACCGAATTGAAAAACAACAACAAAAAAATAAAAAA
GAACGTGAAAACGCAGTCGCCAAATTCAAAGAAGATTTCCCTGATTTTGTGGGCGAACCCAGAGGGA
AAGATATTTTGAAAATGCGTTTGTATGAACAACAACACGGCAAATGTTTGTATTCGGGTCATGATATT
GATATTAATCGATTGAATGAAAAAGGTTATGTTGAAATTGACCATGCCCTGCCATTTTCACGGACTTGG
GATGATAGTCAAAATAATAAAGTTTTGGTACTTGGCAGCGAAAACCAAAATAAACGCAATCAAACGC
CTGATGAATATTTGGACGGTGCAAACAATAGCCAACGTTGGCTTGAATTTCAAGCGCGTGTACAAACT
TGTCATTTTTCTTACGGTAAAAAACAACGCATTCAATTAGCCAAATTAGACGATGAAACCGAAAAAGG
ATTTTTAGAACGCAATCTAAATGATACGCGGTATATTGCTCGTTTTATGTGTCAATTTGTCCAAGAAAA
TTTATATTTGACAGGTAAAGGAAAACGTCTTGTTTTTGCATCAAACGGCGGAATGACCGCAACATTGA
GAAATTTATGGGGTTTGAGAAAAGTCCGTGAAGACAACGACCGCCATCATGCTCTTGATGCGATTGTG
GTGGCGTGTTCCACTGCTTCTATGCAACAAAAAATAACCAAAGCATTTCAACGCCATGAAAGCATTGA
ATATGTGGATACCGAAACGGGCGAAGTAAAATTTCGTATTCCACAGCCTTGGGATTTTTTCCGTCAGG
AAGTGATGATTCGTGTGTTCAGCGACCAACCGTGTGAAGATTTGGTAGAAAAATTGTCGGCTCGTCCC
GAAGCTTTGCATGACAACGTAACGCCTTTATTTGTCTCGCGTGCACCAAATCGCAAAATGTCGGGGCA
AGGGCATTTGGAAACCATCAAATCTGCAAAAAGGCTGTCTGAAGAAAACAGTATGGTTAAAAAACCA
TTAACCACATTGAAATTAAAAGATATTCCAGAAATCGTAGGCTACCCGAGTCGTGAACCTCAATTGTA
TGCCGCATTGAAAACACGTTTAGAAACGCATGATGATGACCCAATTAAAGCCTTTGCCAAACCCTTTT
ACAAACCCAATAAAAATGGTGAATTGGGGGCGTTGGTTCGATCGGTGCGTGTGAAAGGTGTACAAAA
TACGGGTGTAATGGTTCATGATGGCAAAGGCATTGCCGATAATGCCACAATGGTTCGTGTTGATGTCT
ATACCAAAGCGGGCAAAAATTACCTTGTTCCTGTGTATGTTTGGCAGGTGGCTCAAGGAATTTTGCCA
AATCGGGCGGTTACTTCTGGCAAAAGTGAAGCAGATTGGGATTTAATTGATGAAAGTTTTGAATTTAA
ATTTTCGCTGTCTCGTGGGGATTTAGTGGAAATGATTAGCAATAAAGGAAGAATTTTTGGTTATTACAA
TGGGTTAGATCGTGCAAATGGAAGTATTGGGATTCGTGAACATGATTTGGAAAAGTCCAAAGGAAAA
GATGGTGTTCATCGTGTTGGCGTGAAAACCGCCACCGCATTCAACAAATACCACGTTGACCCACTTGG
TAAAGAAATTCATCGGTGTTCATCTGAACCACGCCCCACATTAAAAATCAAATCCAAGAAATAA

Figure 29

MEKFHYVLGLDLGIASVGWAAIEIDKETETSIGLLDCGVRTFERAEVPKTGDSLAKARRE
ARSTRRLIRRRSHRLLRLKRLLKREIFRQPETFKDLPINAWQLRVKGLDSRLNEYEWAAV
LLHLVKHRGYLSQRKSEMSETDSKSEMGRLLAGVAENHQLLQQEQYRTPAELALKKFV
KHFRNKGGDYAHTFNRLDLQAELHLLFQKQRELGNPFTSPELERQVDDLLMTQRSALQ
GDAILKMLGHCGFEPEQFKAAKNTFSAERFIWLTKLNNLRIQDQGKERALTADERTKLL
DEPYKKSKLTYAQVRKLLSLPQTAIFKGLRYDLEHDKKAENSTLMEMKSYHNIRQTLEK
SGLKTEWQSIATQPEILDAIGTAFSIYKTDEDISHELKTCRLPENVLNELLKNINFDGFIQL
SLTALRKILPLMEQGYRYDEACTQIYGNHHSGSLQQESKQFLPHIPIDDVRNPVVFRTLT
QARKVVNAIIRRYGSPARVHIEMARELGKSKSDRDRIEKQQQKNKKERENAVAKFKED
FPDFVGEPRGKDILKMRLYEQQHGKCLYSGHDIDINRLNEKGYVEIDHALPFSRTWDDS
QNNKVLVLGSENQNKRNQTPDEYLDGANNSQRWLEFQARVQTCHFSYGKKQRIQLAK
LDDETEKGFLERNLNDTRYIARFMCQFVQENLYLTGKGKRLVFASNGGMTATLRNLWG
LRKVREDNDRHHALDAIVVACSTASMQQKITKAFQRHESIEYVDTETGEVKFRIPQPWD
FFRQEVMIRVFSDQPCEDLVEKLSARPEALHDNVTPLFVSRAPNRKMSGQGHLETIKSA
KRLSEENSMVKKPLTTLKLKDIPEIVGYPSREPQLYAALKTRLETHDDDPIKAFAKPFYK
PNKNGELGALVRSVRVKGVQNTGVMVHDGKGIADNATMVRVDVYTKAGKNYLVPVY
VWQVAQGILPNRAVTSGKSEADWDLIDESFEFKFSLSRGDLVEMISNKGRIFGYYNGLD
RANGSIGIREHDLEKSKGKDGVHRVGVKTATAFNKYHVDPLGKEIHRCSSEPRPTLKIKS
KK*

Figure 30

ATGGAGAAGTTCCACTACGTGCTGGGACTGGATCTGGGAATCGCAAGCGTGGGATGGGCAGCAATCGAGATCGATAAGGAGACCGAGACAT
CCATCGGCCTGCTGGACTGCGGCGTGAGGACCTTTGAGAGGGCAGAGGTGCCTAAGACAGGCGACAGCCTGGCAAAGGCAAGGAGAGAGGC
AAGGTCTACAAGGCGCCTGATCCGGAGAAGGAGCCACAGGCTGCTGCGGCTGAAGAGACTGCTGAAGCGGGAGATCTTTAGACAGCCAGAG
ACCTTCAAGGATCTGCCCATCAACGCATGGCAGCTGAGGGTGAAGGGACTGGACTCTCGGCTGAATGAGTACGAGTGGGCAGCCGTGCTGCT
GCACCTGGTGAAGCACAGGGGCTATCTGAGCCAGCGCAAGTCCGAGATGTCTGAGACCGACTCTAAGAGCGAGATGGGCAGGCTGCTGGCA
GGAGTGGCCGAGAACCACCAGCTGCTGCAGCAGGAGCAGTACAGGACCCCAGCAGAGCTGGCCCTGAAGAAGTTTGTGAAGCACTTCCGCA
ACAAGGGCGGCGATTATGCCCACACATTCAATAGGCTGGACCTGCAGCCAGAGCTGCACCTGCTGTTCAGAAGCAGAGAGAGCTGGGCAAC
CCCTTCACCTCTCCTGAGCTGGAGCGCCAGGTGGACGATCTGCTGATGACACAGCGGAGCGCCCTGCAGGGCGATGCAATCCTGAAGATGCT
GGGCCACTGTGGCTTTGAGCCTGAGCAGTTCAAGGCCGCCAAGAATACCTTTAGCGCCGAGAGATTCATCTGGCTGACAAAGCTGAACAATC
TGAGGATCCAGGACCAGGGCAAGGAGAGAGCCCTGACCGCCGATGAGAGGACAAAGCTGCTGGACGAGCCTTACAAGAAGTCTAAGCTGAC
CTATGCCCAGGTGAGGAAGCTGCTGAGCCTGCCTCAGACAGCCATCTTCAAGGGCCTGCGCTACGATCTGGAGCACGACAAGAAGGCCGAGA
ACTCTACCCTGATGGAGATGAAGAGCTATCACAATATCCGGCAGACACTGGAGAAGTCCGGCCTGAAGACCGAGTGGCAGTCTATCGCCACA
CAGCCAGAGATCCTGGACGCAATCGGAACCGCCTTTTCCATCTACAAGACAGATGAGGACATCTCTCACGAGCTGAAGACCTGCAGACTGCC
TGAGAACGTGCTGAATGAGCTGCTGAAGAACATCAATTTTGATGGCTTCATCCAGCTGAGCCTGACCGCCCTGCGCAAGATCCTGCCACTGAT
GGAGCAGGGCTACCGGTATGACGAGGCCTGTACACAGATCTACGGCAACCACCACTCCGGCTCTCTGCAGCAGGAGTCCAAGCAGTTTCTGC
CTCACATCCCAATCGACGATGTGCGGAACCCAGTGGTGTTCAGAACCCTGACACAGGCCAGGAAGGTGGTGAATGCCATCATCCGCCGGTAT
GGATCTCCAGCAAGGGTGCACATCGAGATGGCAAGGGAGCTGGGCAAGAGCAAGTCCGATAGAGACAGGATCGAGAAGCAGCAGCAGAAG
AACAAGAAGGAGAGGGAGAATGCCGTGGCCAAGTTCAAGGAGGATTTTCCAGACTTCGTGGGAGAGCCTAGGGGCAAGGATATCCTGAAGA
TGCGGCTGTACGAGCAGCAGCACGGCAAGTGCCTGTATTCCGGCCACGATATCGACATCAACCGGCTGAATGAGAAGGGCTACGTGGAGATC
GACCACGCCCTGCCTTTTAGCAGAACCTGGGACGATTCCCAGAACAATAAGGTGCTGGTGCTGGGCAGCGAGAACCAGAATAAGCGCAATCA
GACACCAGATGAGTACCTGGACGGCGCCAACAATTCCCAGAGATGGCTGGAGTTTCAGGCCAGGGTGCAGACCTGCCACTTCTCTTATGGCA
AGAAGCAGAGGATCCAGCTGGCCAAGCTGGACGATGAGACCGAGAAGGGCTTCCTGGAGCGCAACCTGAATGATACAAGGTACATCGCCCG
GTTCATGTGCCAGTTCGTGCAGGAGAACCTGTATCTGACCGGCAAGGGCAAGCGCCTGGTGTTTGCCTCCAACGGCGGCATGACCGCCACACT
GCGGAATCTGTGGGGCCTGAGGAAGGTGCGCGAGGATAATGACAGACACCACGCACTGGACGCAATCGTGGTGGCATGCAGCACCGCATCC
ATGCAGCAGAAGATCACAAAGGCCTTTCAGCGGCACGAGAGCATCGAGTATGTGGATACCGAGACAGGCGAGGTGAAGTTCAGAATCCCCC
AGCCTTGGGACTTCTTTCGCCAGGAAGTGATGATCCGGGTGTTTTCCGATCAGCCATGTGAGGACCTGGTGGAGAAGCTGTCTGCCAGGCCAG
AGGCCCTGCACGATAACGTGACCCCTCTGTTCGTGAGCAGGGCACCAAATAGAAAGATGTCCGGCCAGGGCCACCTGGAGACAATCAAGTCC
GCCAAGCGCCTGTCCGAGGAGAACTCTATGGTGAAGAAGCCCCTGACCACACTGAAGCTGAAGGACATCCCTGAGATCGTGGGCTACCCATC
TAGAGAGCCCCAGCTGTATGCCGCCCTGAAGACCAGGCTGGAGACACACGACGATGACCCAATCAAGGCCTTTGCCAAGCCTTTCTACAAGC
CAAACAAGAATGGAGAGCTGGGCGCCCTGGTGCGGTCCGTGAGAGTGAAGGGCGTGCAGAACACAGGCGTGATGGTGCACGATGGCAAGGG
CATCGCCGACAATGCCACAATGGTGCGGGTGGACGTGTATACAAAGGCCGGCAAGAACTACCTGGTGCCCGTGTACGTGTGGCAGGTGGCAC
AGGGAATCCTGCCAAATAGAGCCGTGACCTCTGGCAAGAGCGAGGCCGATTGGGACCTGATCGATGAGAGCTTCGAGTTTAAGTTCTCTCTG
AGCAGAGGCGACCTGGTGGAGATGATCTCCAACAAGGGCAGGATCTTCGGCTACTATAACGGCCTGGATAGAGCCAATGGCAGCATCGGCAT
CAGGGAGCACGATCTGGAGAAGTCCAAGGGCAAGGACGGAGTGCACAGGGTGGGAGTGAAGACCGCAACAGCCTTTAATAAGTACCACGTG
GACCCCCTGGGCAAGGAGATCCACAGATGTAGCTCCGAGCCAAGGCCCACCCTGAAGATCAAGAGCAAGAAGGGCACCGGCGGG
CCCAAGAAGAAGAGGAAGGTATACCATCGATGTTCTGACTATGGGCATCCTATGACGTCCGGACTATGCAGATGATCTTAT
GACTTCAGATTGCCTGGATCCGCCCCTCCGGCAGCTAAGAAAAAGAACTGGATTTCGAATCCGGATAA

Figure 31

MEKPHYVLGLDLGIASVGWAAIEIDKETETSIGLLDCGVRTFERAEVPKTGDSLAKARREARSTRRLIRRRSHRLLRLKRLLKREIFRQPETFKDLPIN
AWQLRVKGLDSRLNEYEWAAVLLHLVKHRGYLSQRKSEMSETDSKSEMGRLLAGVAENHQLLQQEQYRTPAELALKKFVKHFRNKGGDYAHTF
NRLDLQAELHLLFQKQRELGNPFTSPELERQVDDLLMTQRSALQGDAILKMLGHCGFEPEQFKAAKNTFSAERFIWLTKLANNLRIQDQGKERALTA
DERTKLLDEPYKKSKLTYAQVRKLLSLPQTAIFKGLRYDLEHDKKAENSTLMEMKSYHNIRQTLEKSGLKTEWQSIATQPEHLDAIGTAFSIYKTDED
ISHELKTCRLPENVLNELLKNINFDGFIQLSLTALRKILPLMEQGYRYDEACTQIYGNHHSGSLQQESKQFLPHIPDDVRNPVVFRTLTQARKVVNAII
RRYGSPARVHIEMARELGKSKSDRDRIEKQQQKNKKERENAVAKFKEDFPDFVGEPRGKDILKMRLYEQQHGKCLYSGHDIDINRLNEKGYVEIDH
ALPFSRTWDDSQNNKVLVLGSENQNKRNQTPDEYLDGANNSQRWLEFQARVQTCHFSYGKKQRIQLAKLDDETEKGFLERNLNDTRYIARFMCQF
VQENLYLTGKGKRLVFASNGGMTATLRNLWGLRKVREDNDRHHALDAIVVACSTASMQQKITKAFQRHESIEYVDTETGEVKFRIPQPWDFFRQE
VMIRVFSDQPCEDLVEKLSARPEALHDNVTPLFVSRAPNRKMSGQGHLETIKSAKRLSEENSMVKKPLTTLKLKDIPEIVGYPSREPQLYAALKTRLE
THDDDPIKAFAKPFYKPNKNGELGALVRSVRVKGVQNTGVMVHDGKGIADNATMVRVDVYTKAGKNYLVPVYVWQVAQGILPNRAVTSGKSEA
DWDLIDESFEFKFSLSRGDLVEMISNKGRIFGYYNGLDRANGSIGIREHDLEKSKGKDGVHRVGVKTATAFNKYHVDPLGKEIHRCSSEPRPTLKIKS
KKGTGGPKKKRKVYPYDVPDYAGYPYDVPDYAGSYPYDVPDYAGSAPAAKKKLDFESG[8]

Figure 32

Nme2 sgRNA:



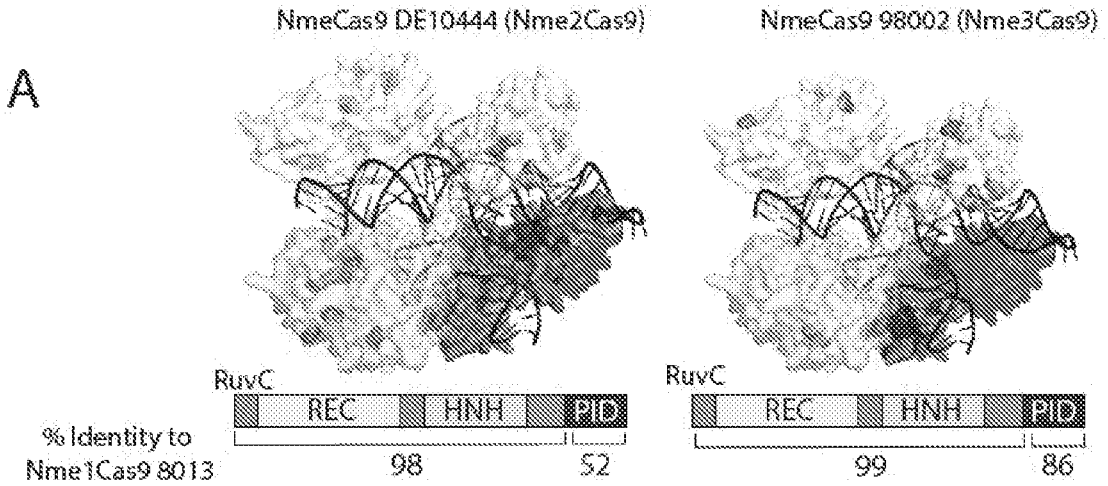
Hpa sgRNA:



Smu sgRNA:



Figure 33


A
NmeCas9 DE10444 (Nme2Cas9)
NmeCas9 98002 (Nme3Cas9)
RuvC
REC
HNH
PID
% Identity to
Nme1Cas9 8013
98
52
99
86

A

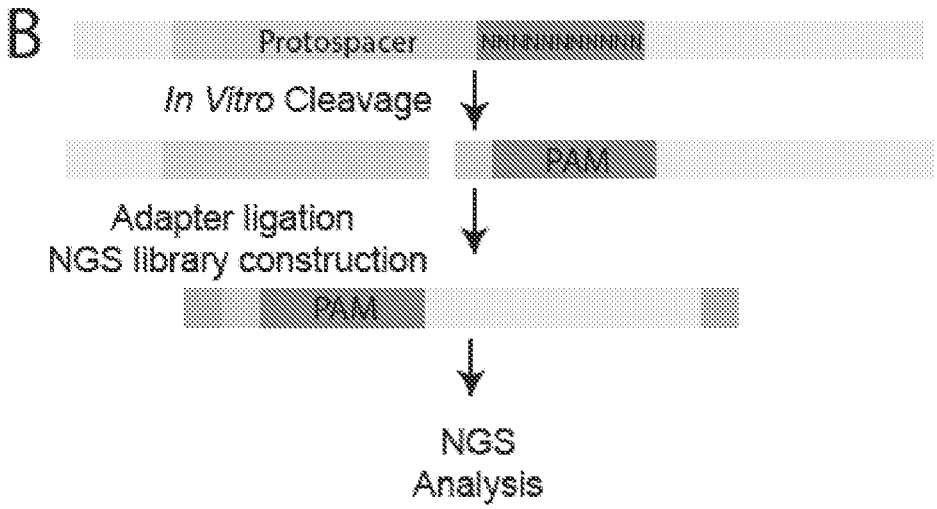

B
Protospacer
In Vitro Cleavage
PAM
Adapter ligation
NGS library construction
PAM
NGS
Analysis

Figure 34

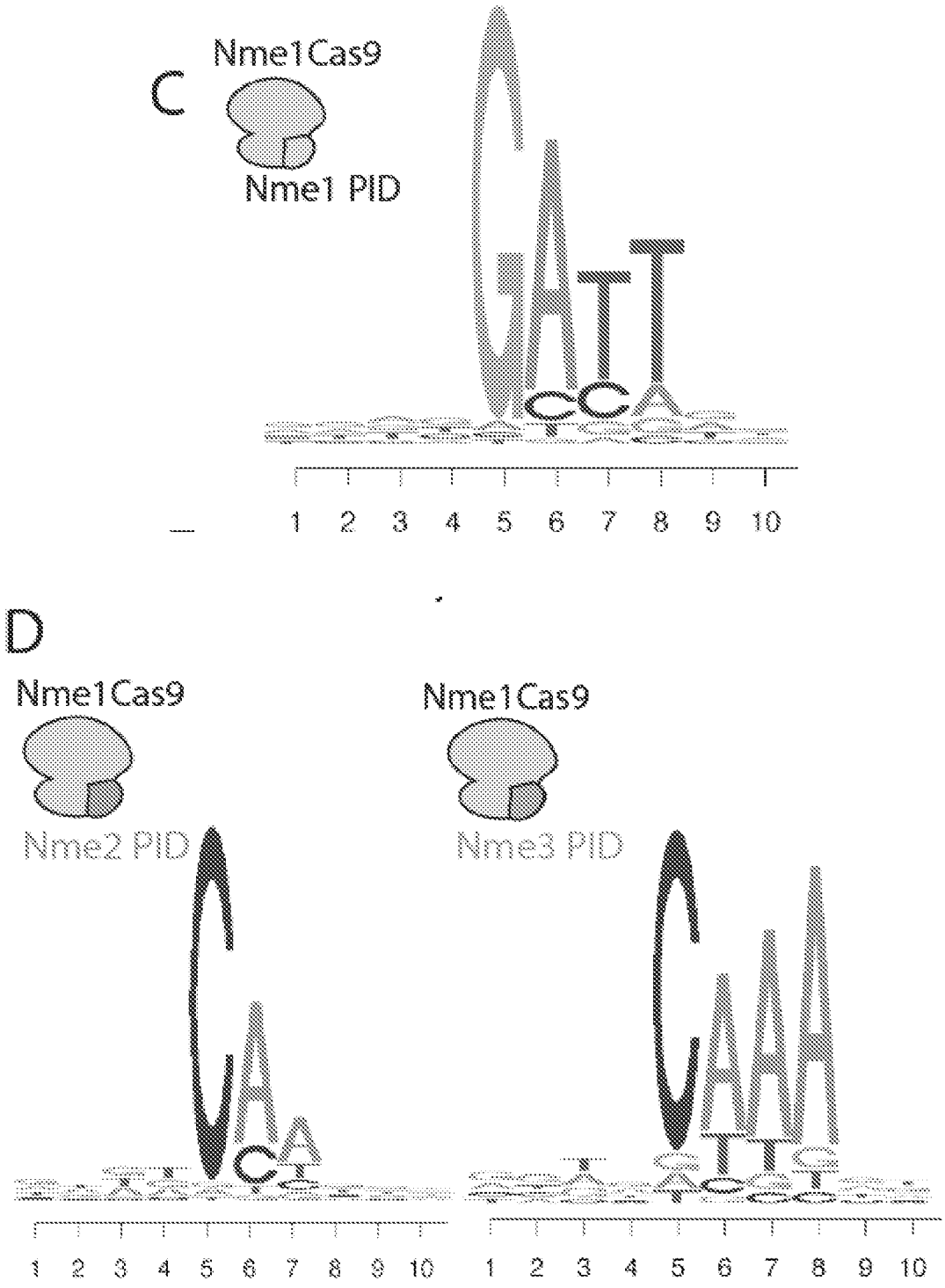


Figure 34 (cont'd)

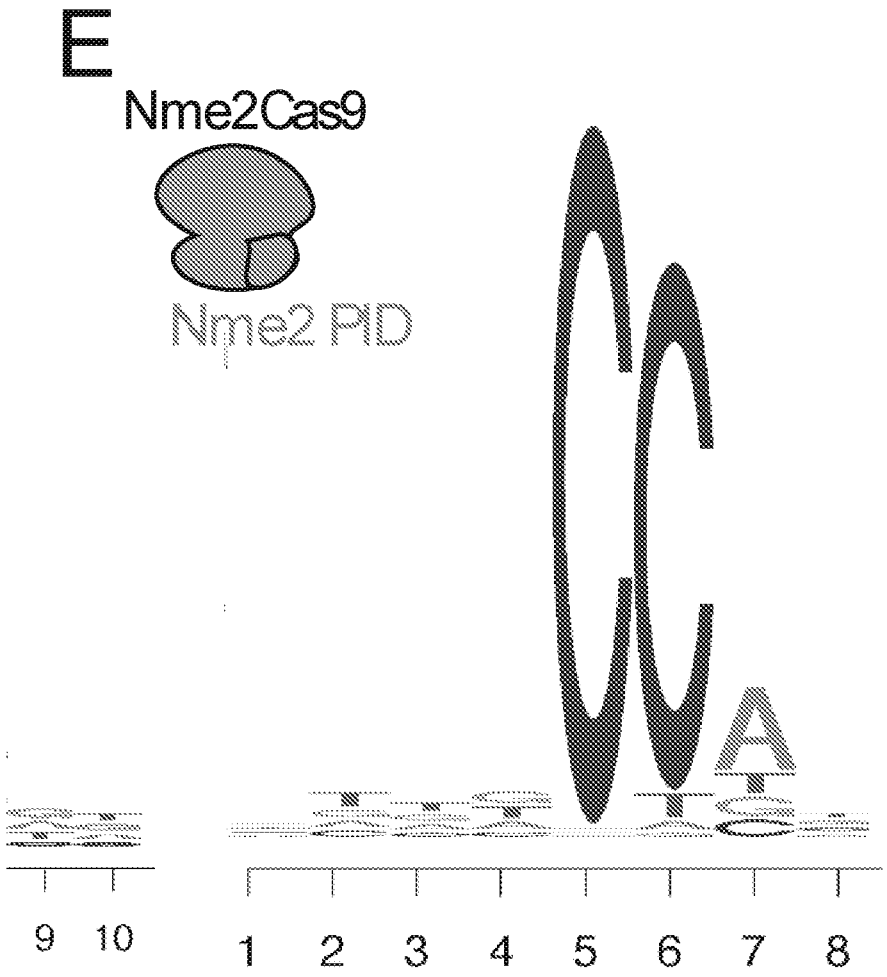


Figure 34 (cont'd)

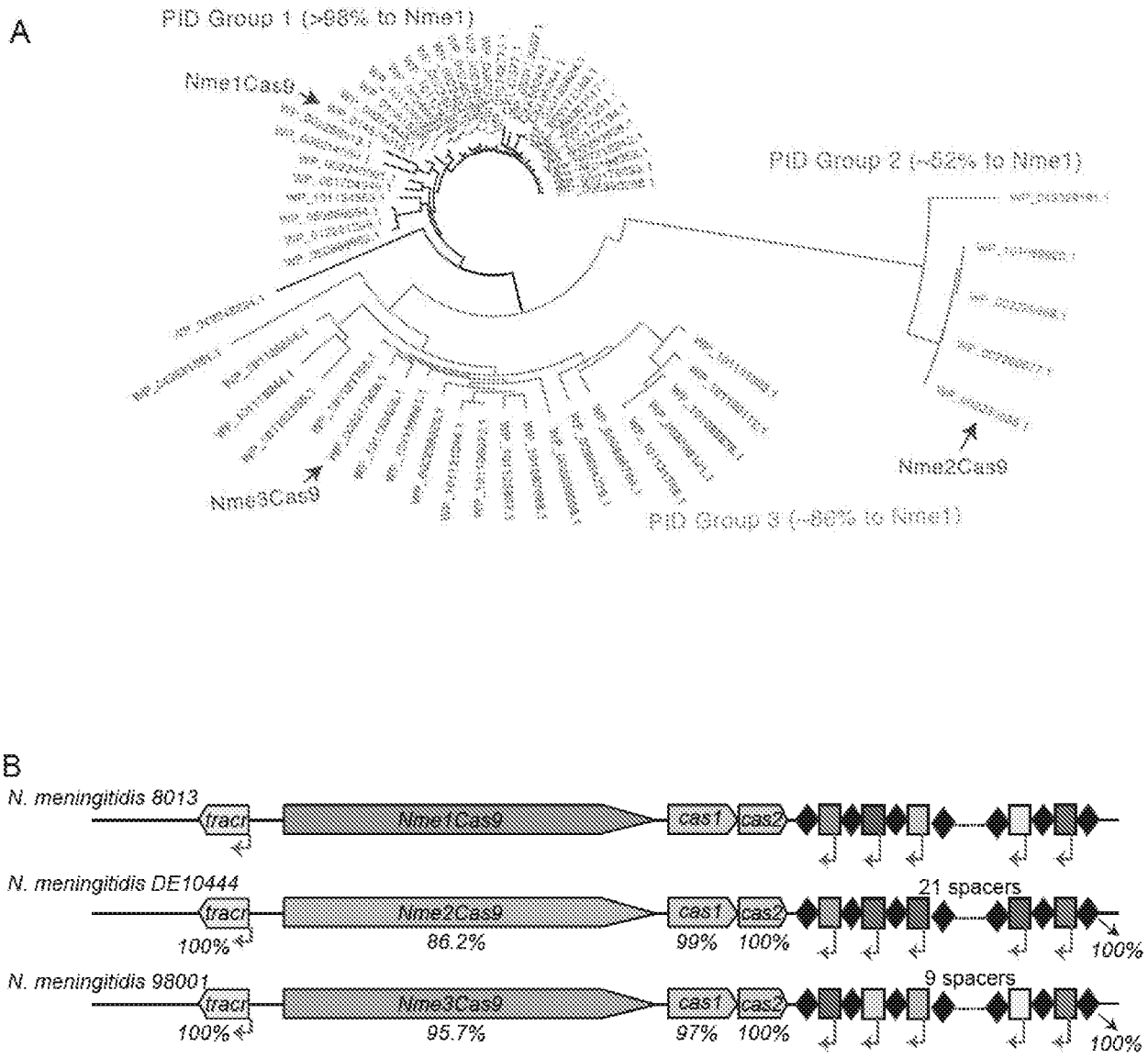

A
PID Group 1 (>68% to Nme1)
Nme1Cas9
PID Group 2 (~62% to Nme1)
Nme2Cas9
Nme3Cas9
PID Group 3 (~60% to Nme1)
B
N. meningitidis 8013
tracr
Nme1Cas9
cas1
cas2
N. meningitidis DE10444
21 spacers
100%
86.2%
99%
100%
100%
N. meningitidis 98001
9 spacers
100%
95.7%
97%
100%
100%

Figure 35

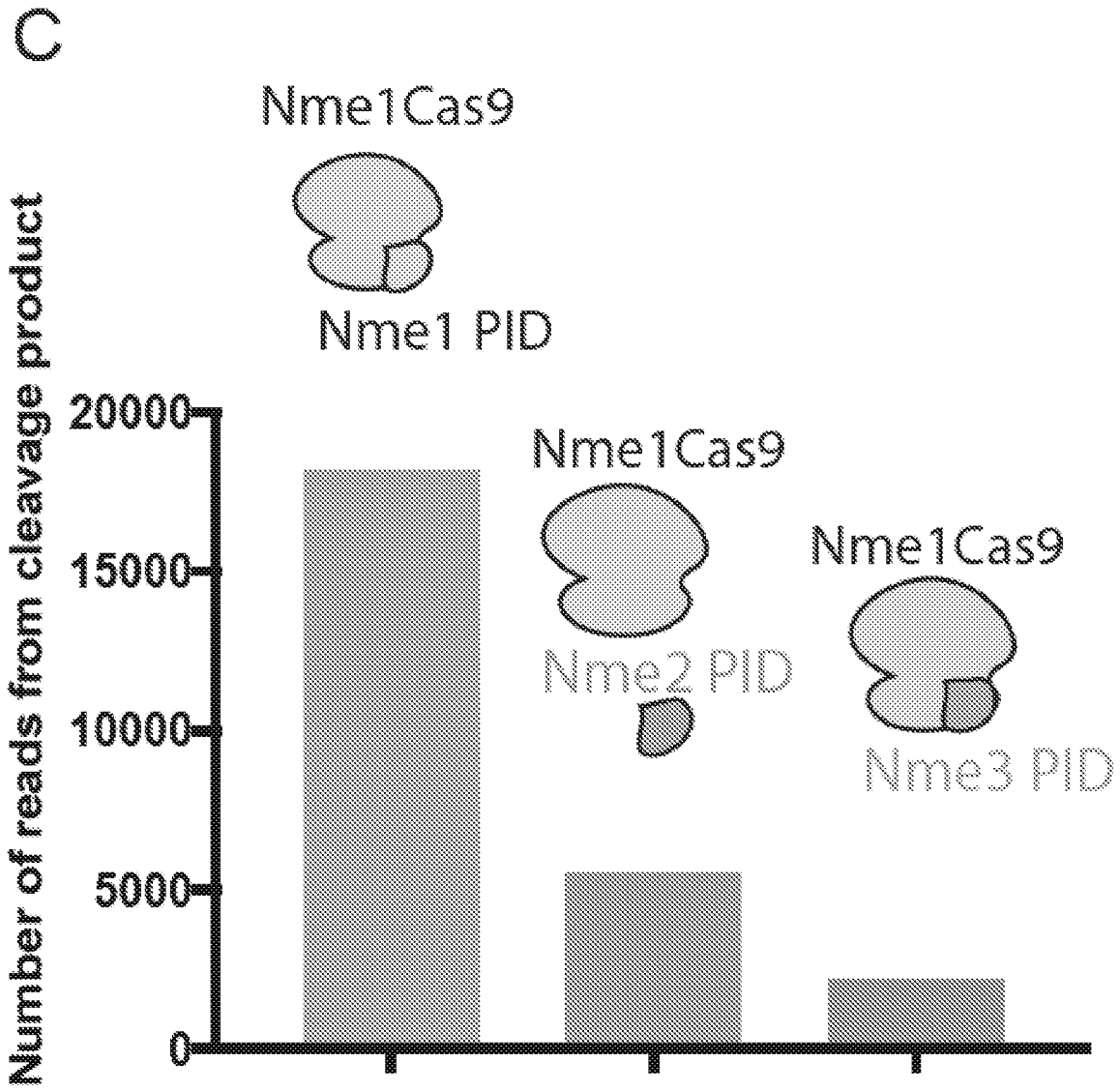


Figure 35 (cont'd)

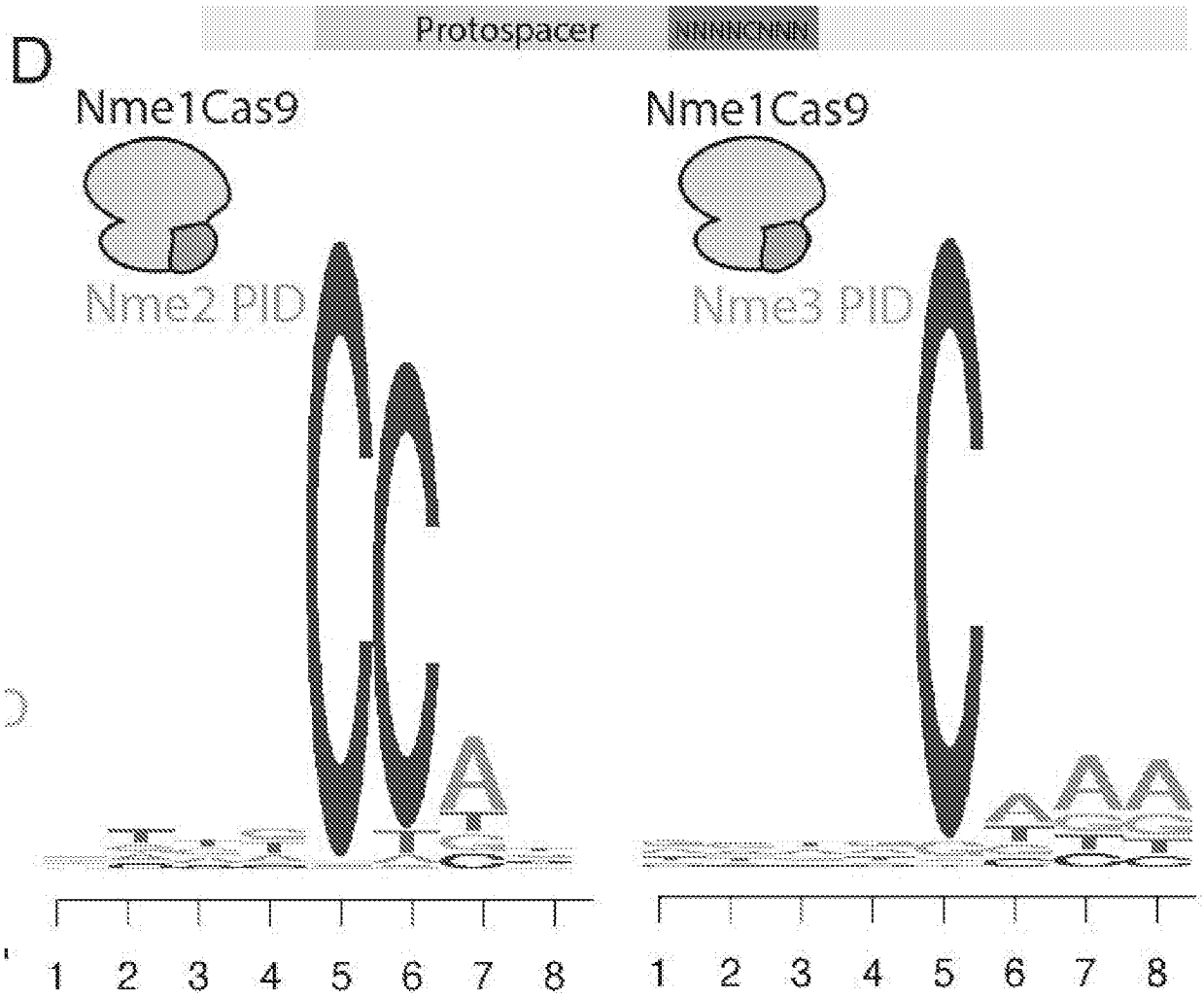


Figure 35 (cont'd)

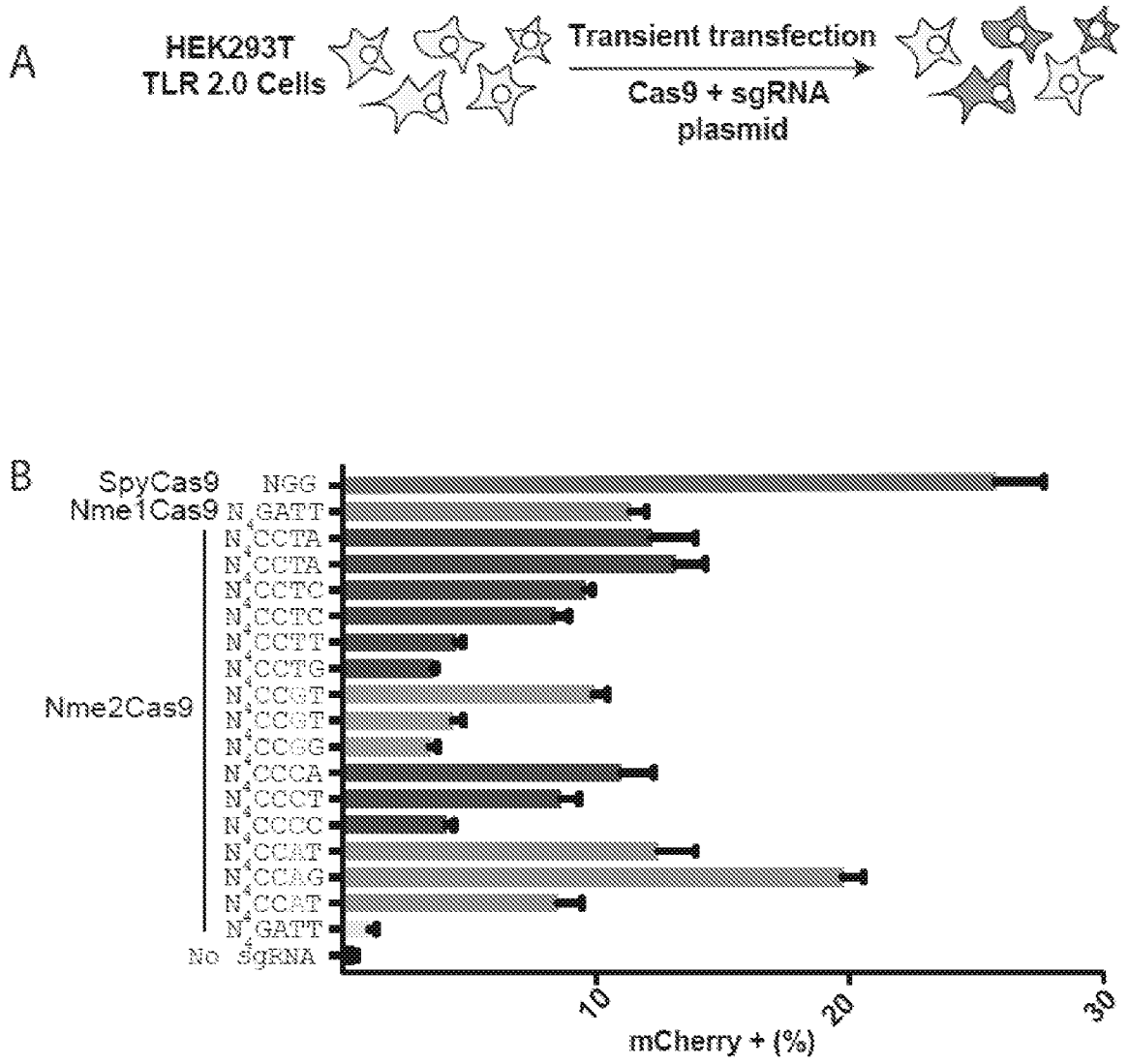
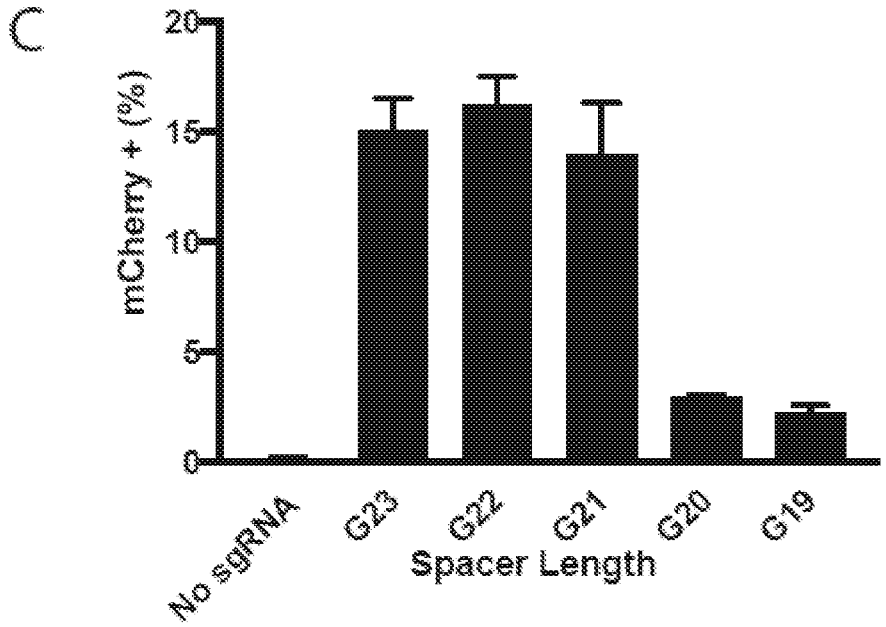

A
HEK293T
TLR 2.0 Cells
Transient transfection
Cas9 + sgRNA
plasmid
B
SpyCas9
Nme1Cas9
Nme2Cas9
NGG
N4GATT
N4CCTA
N4CCTA
N4CCTC
N4CCTC
N4CCTT
N4CCTG
N4CCGT
N4CCGT
N4CCGG
N4CCCA
N4CCCT
N4CCCC
N4CCAT
N4CCAG
N4CCAT
N4GATT
No sgRNA
10
20
30
mCherry + (%)

Figure 36



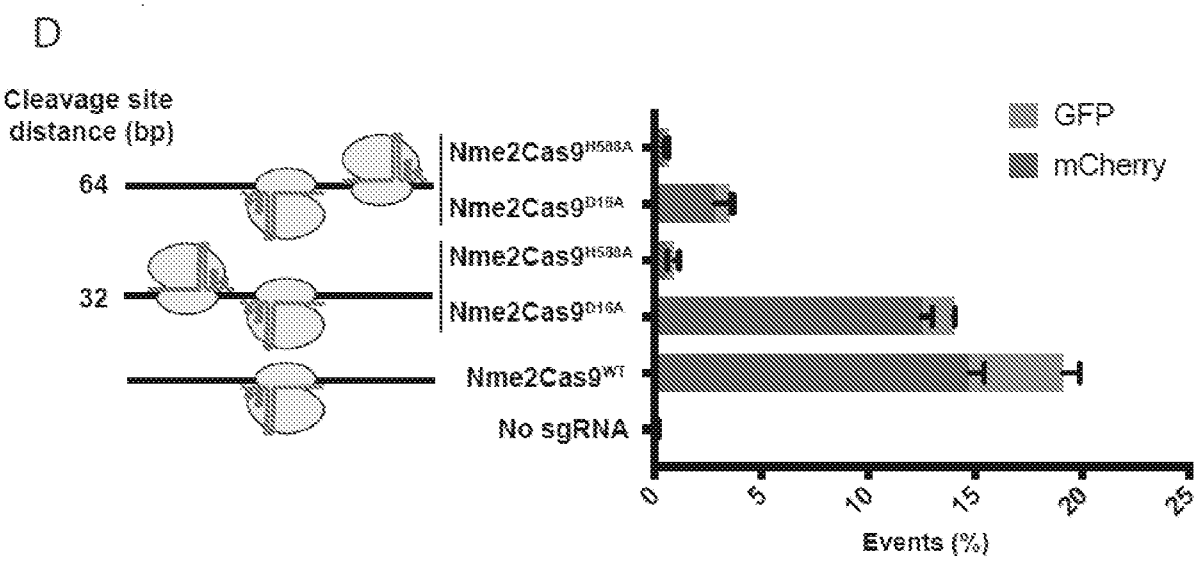


Figure 36 (cont'd)

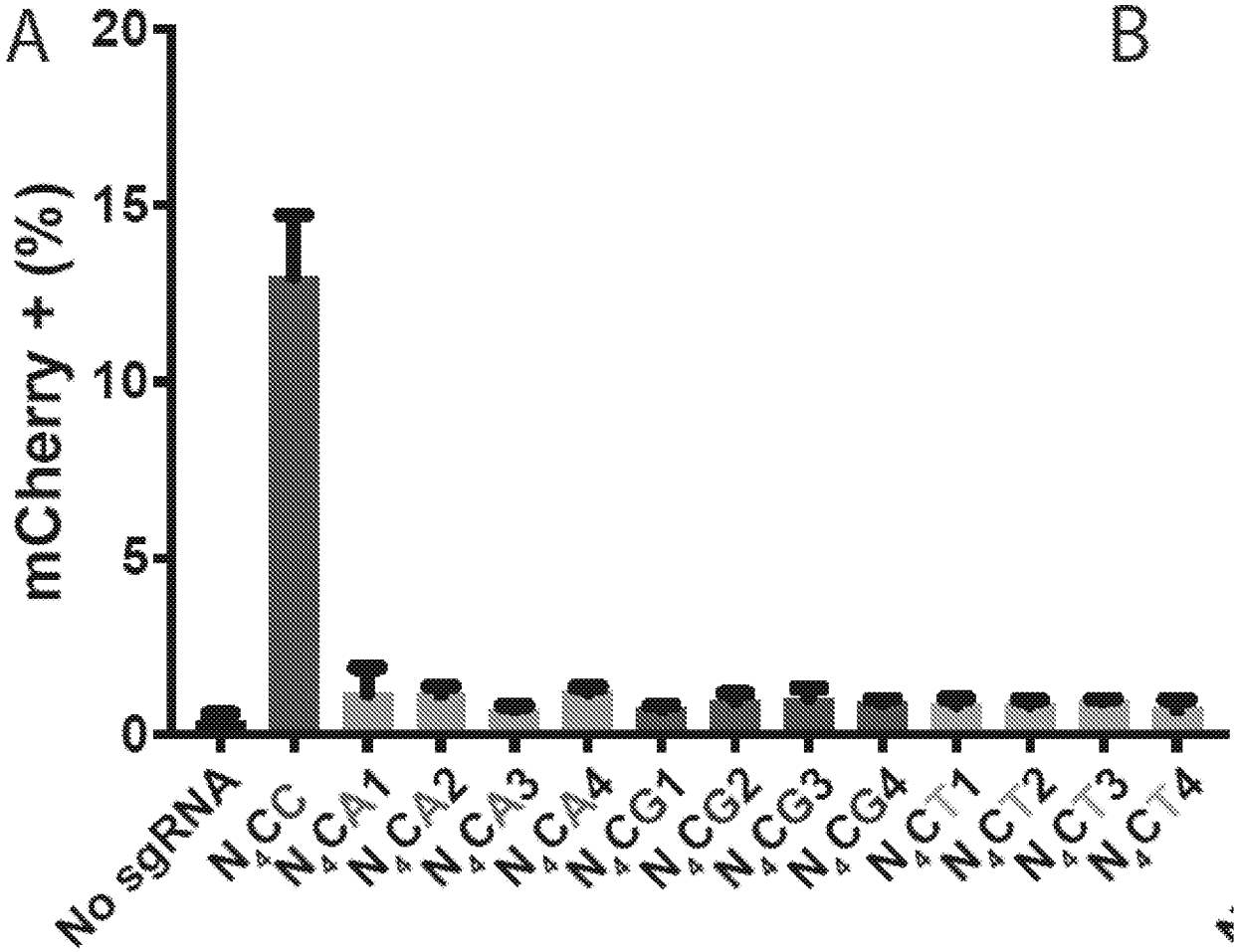

A
B
20
15
10
5
0
mCherry + (%)
No sgRNA
NΔCC
NΔCA1
NΔCA2
NΔCA3
NΔCA4
NΔCG1
NΔCG2
NΔCG3
NΔCG4
NΔCT1
NΔCT2
NΔCT3
NΔCT4

Figure 37

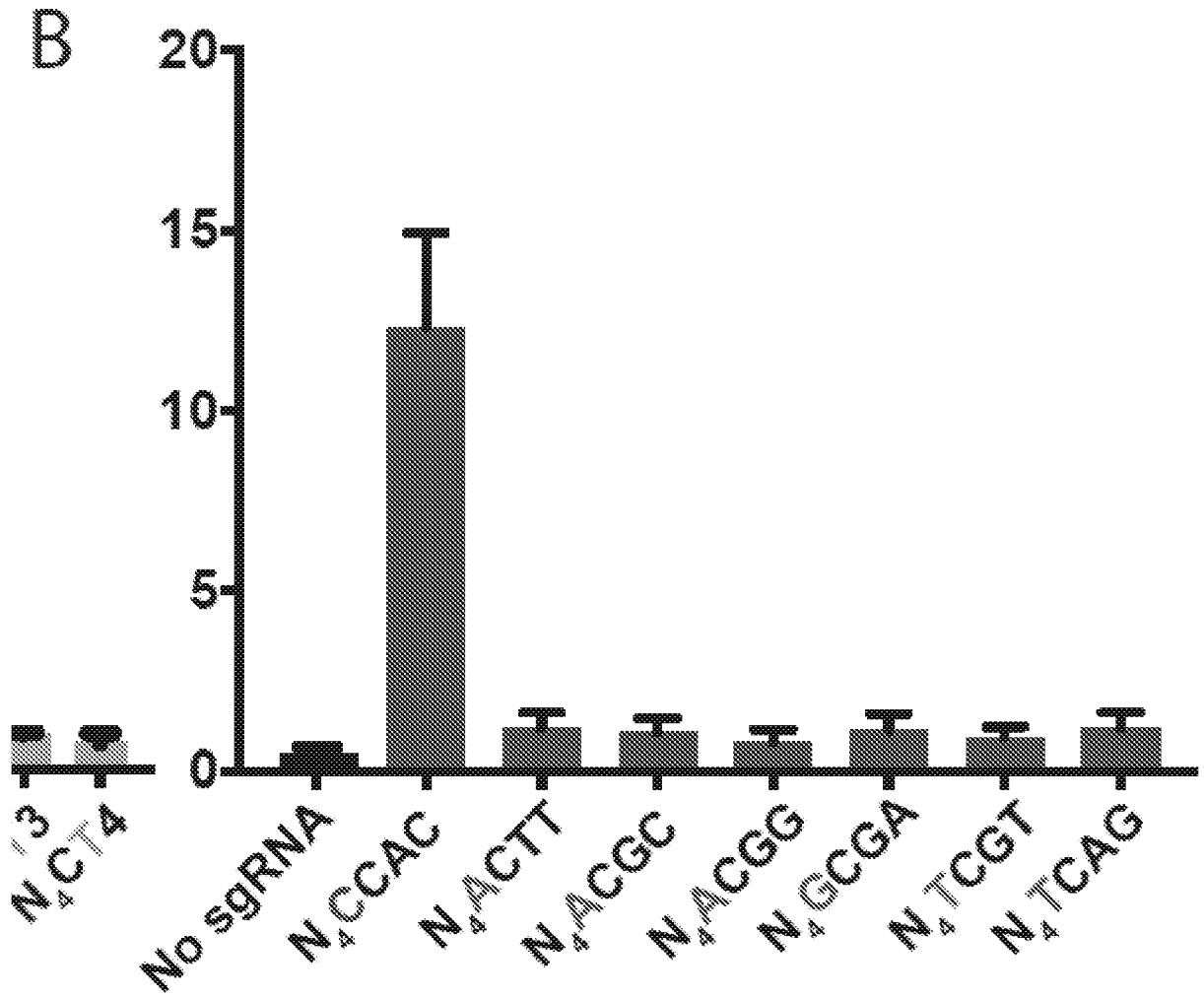


Figure 37 (cont'd)

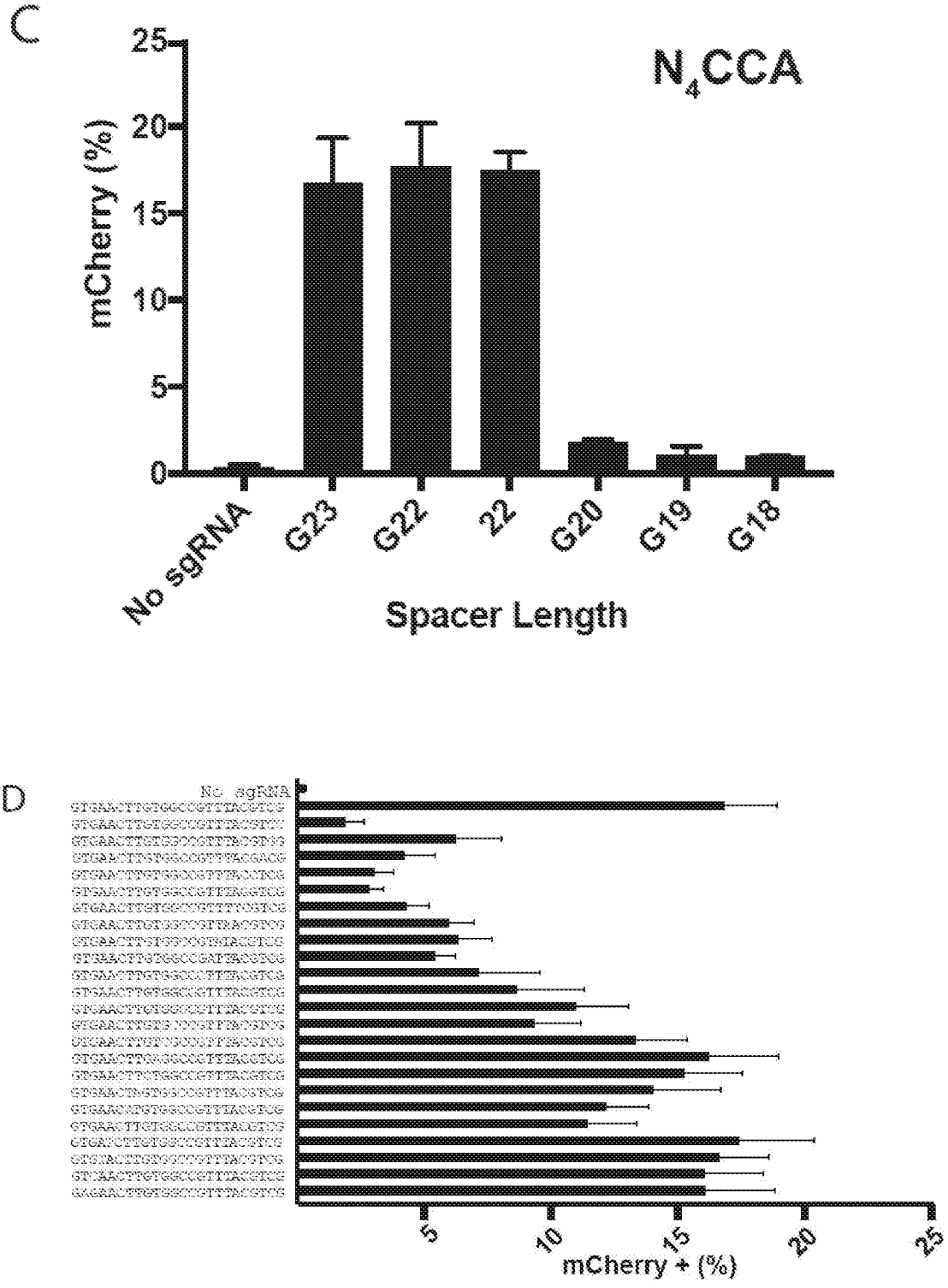


Figure 37 (cont'd)

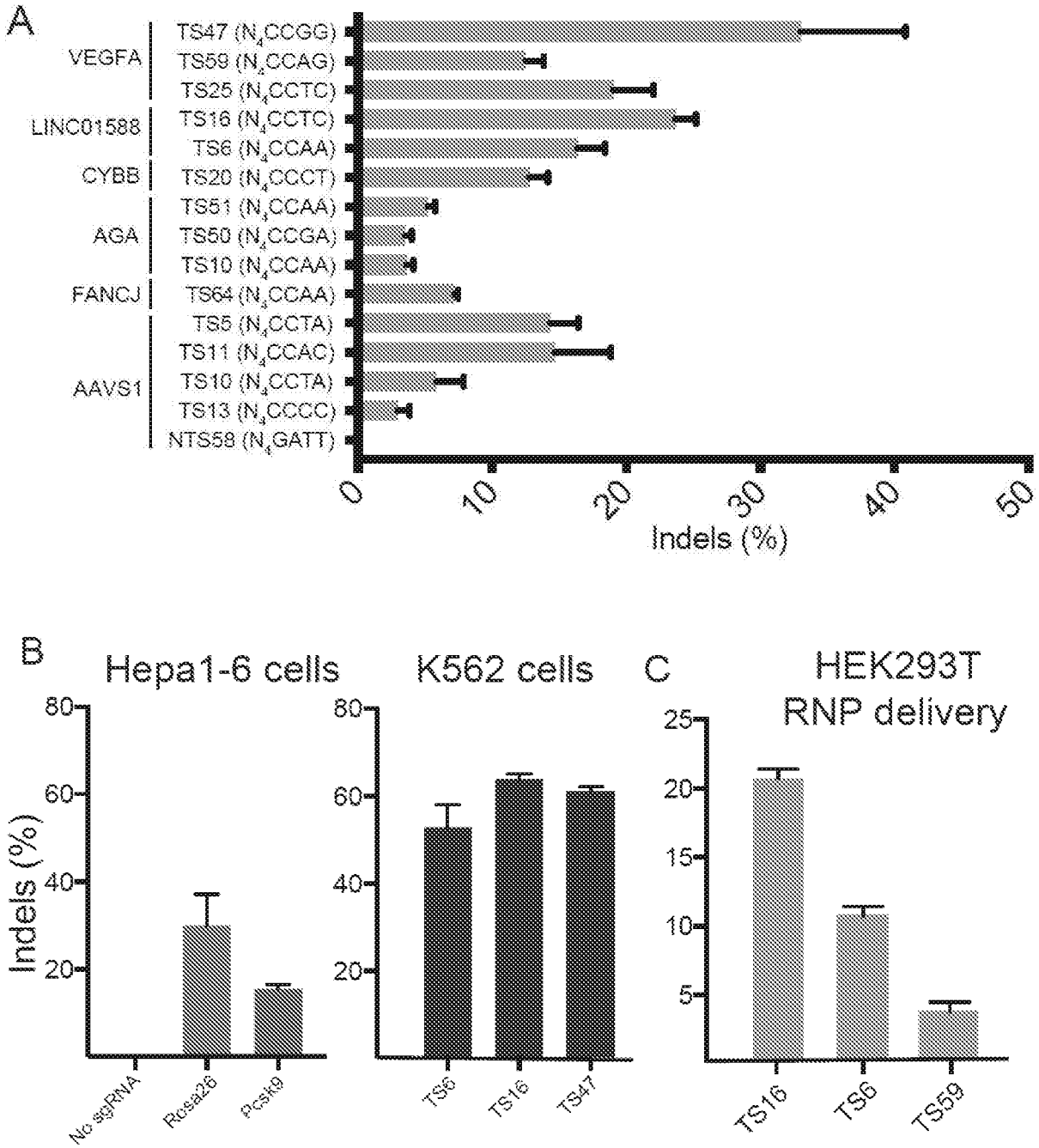

A
VEGFA
LINC01588
CYBB
AGA
FANCJ
AAVS1
TS47 (N4CCGG)
TS59 (N4CCAG)
TS25 (N4CCTC)
TS16 (N4CCTC)
TS6 (N4CCAA)
TS20 (N4CCCT)
TS51 (N4CCAA)
TS50 (N4CCGA)
TS10 (N4CCAA)
TS64 (N4CCAA)
TS5 (N4CCTA)
TS11 (N4CCAC)
TS10 (N4CCTA)
TS13 (N4CCCC)
NTS58 (N4GATT)
0
10
20
30
40
50
Indels (%)
B
Hepa1-6 cells
K562 cells
Indels (%)
80
60
40
20
No sgRNA
Rosa26
Pcsk9
TS6
TS16
TS47
C
HEK293T
RNP delivery
25
20
15
10
5
TS16
TS6
TS59

Figure 38

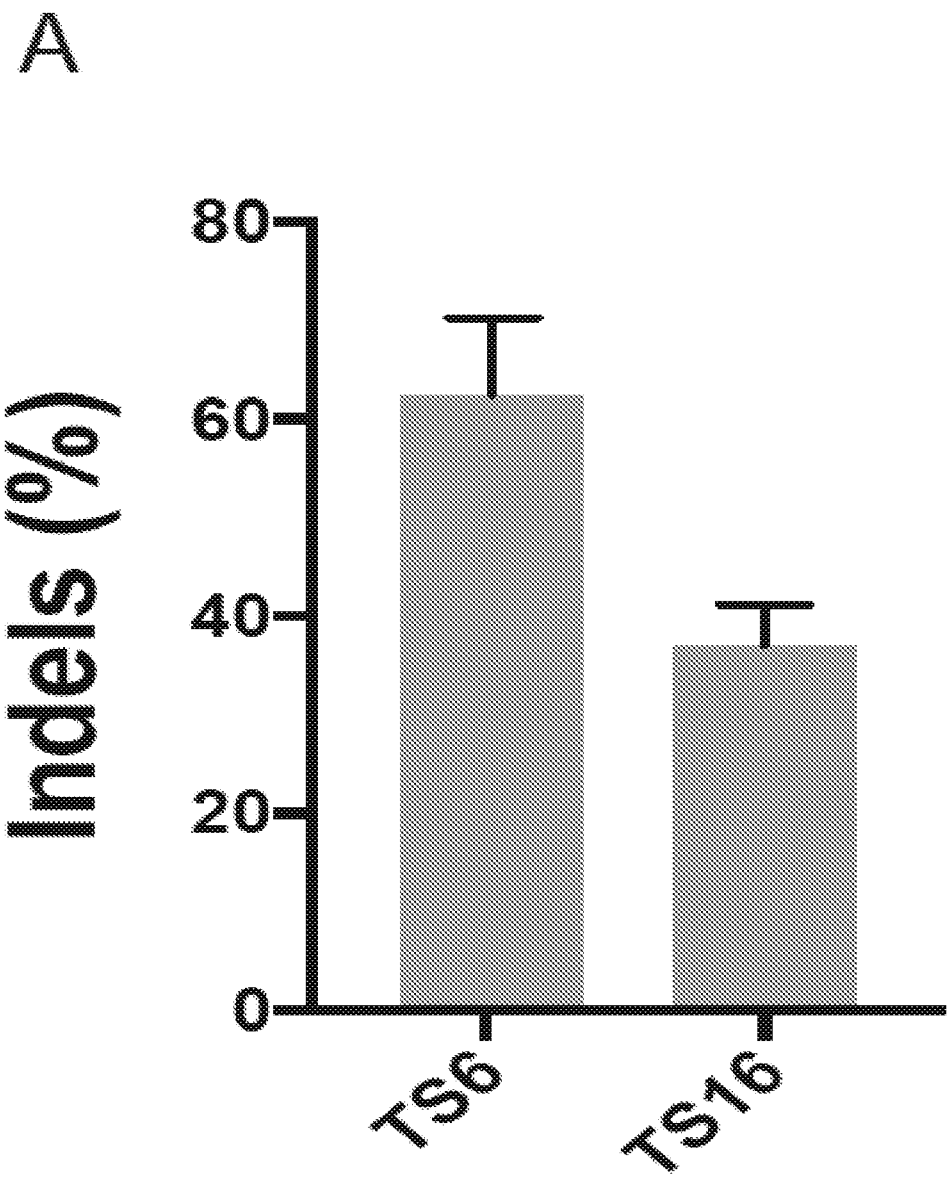


Figure 39

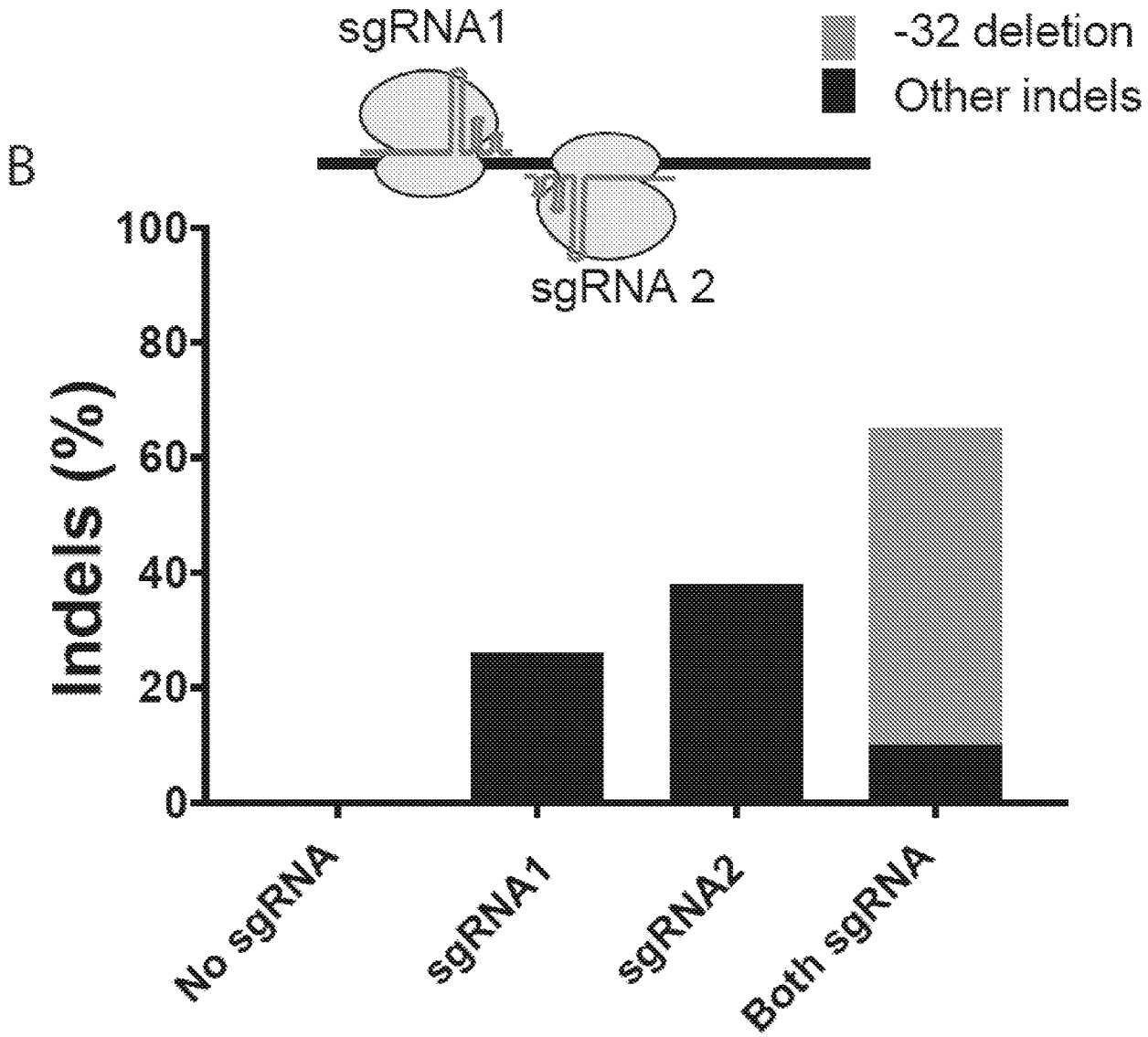


Figure 39 (cont'd)

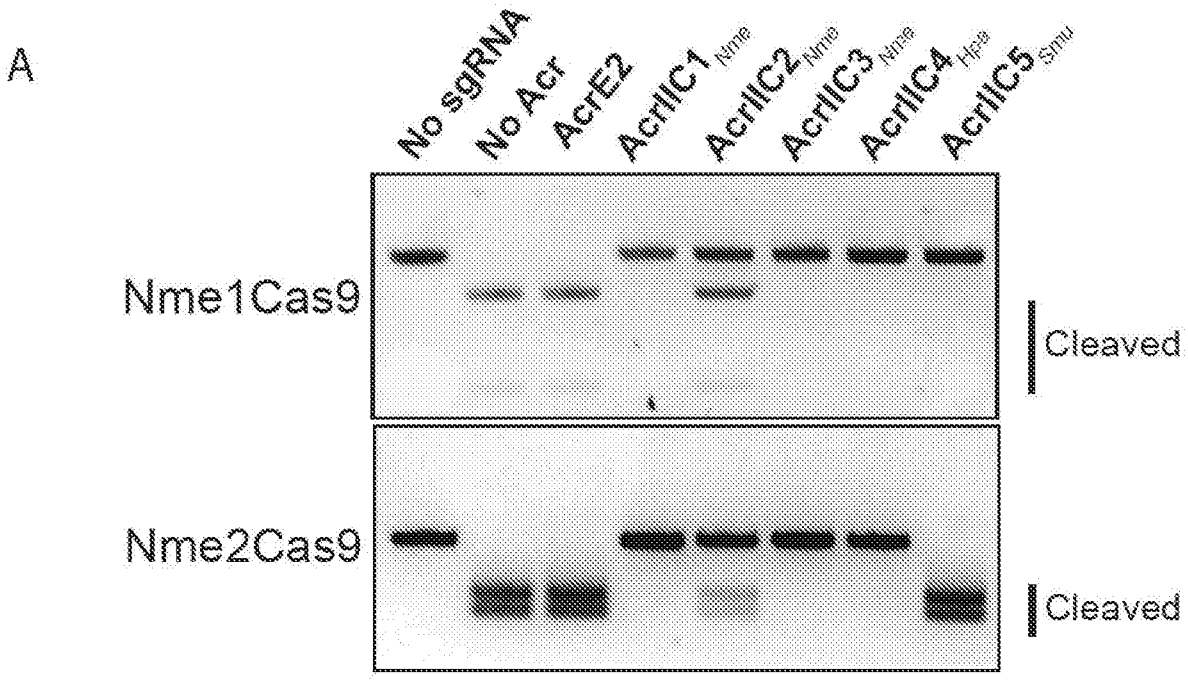

A
No sgRNA
No Acr
AcrE2
AcrIIC1 Nme
AcrIIC2 Nme
AcrIIC3 Nme
AcrIIC4 Hpa
AcrIIC5 Smu
Nme1Cas9
Cleaved
Nme2Cas9
Cleaved

Figure 40

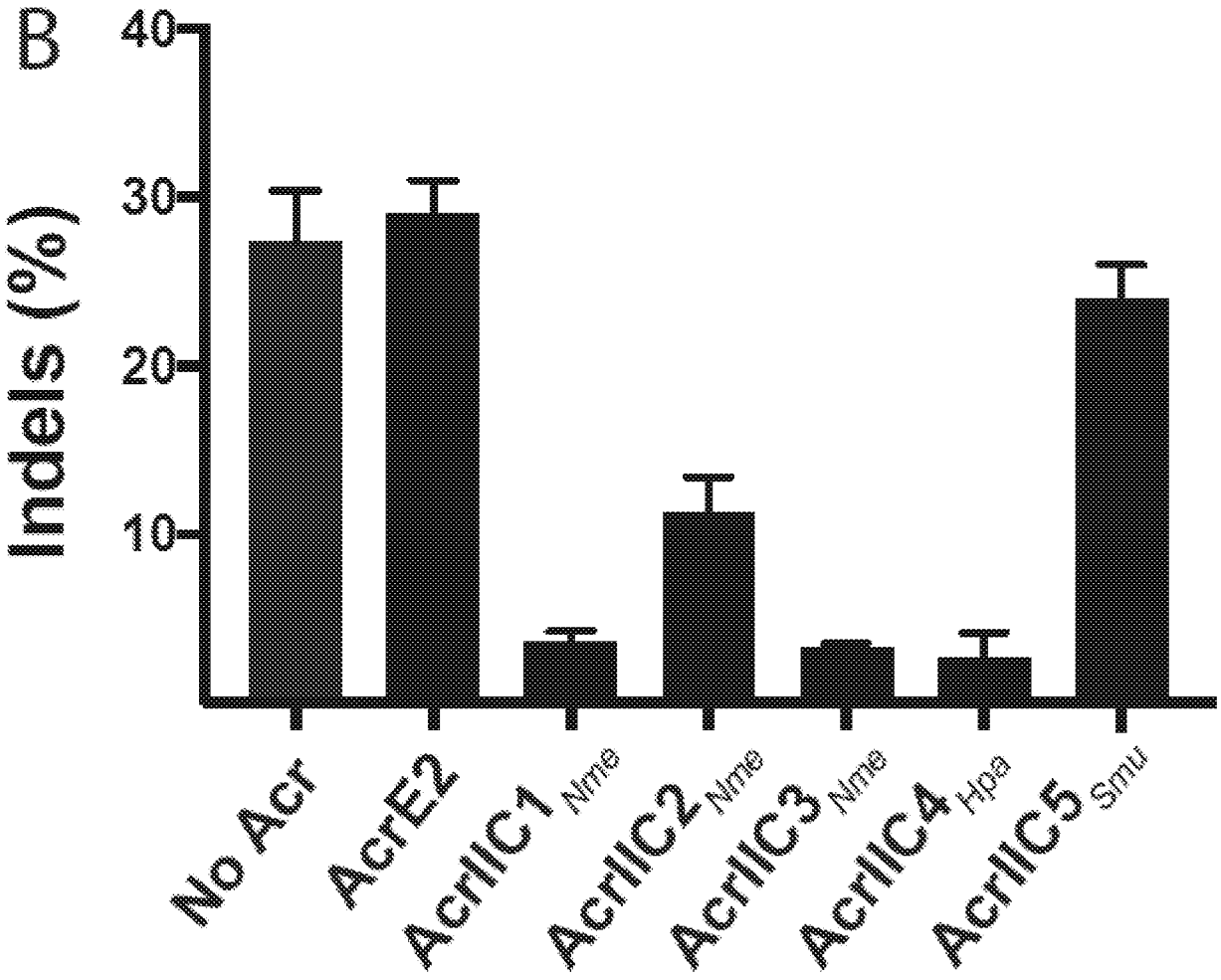


Figure 40 (cont'd)

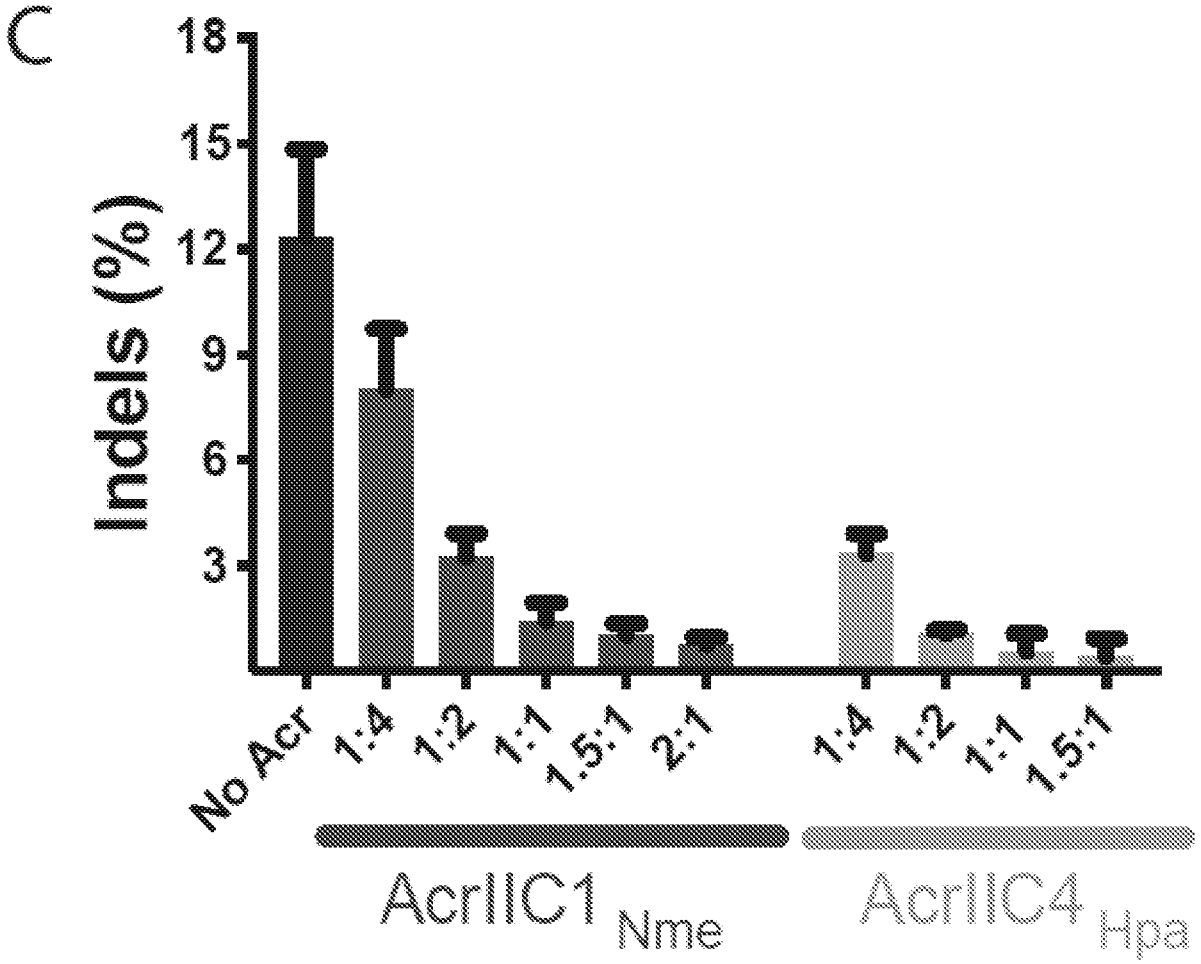


Figure 40 (cont'd)

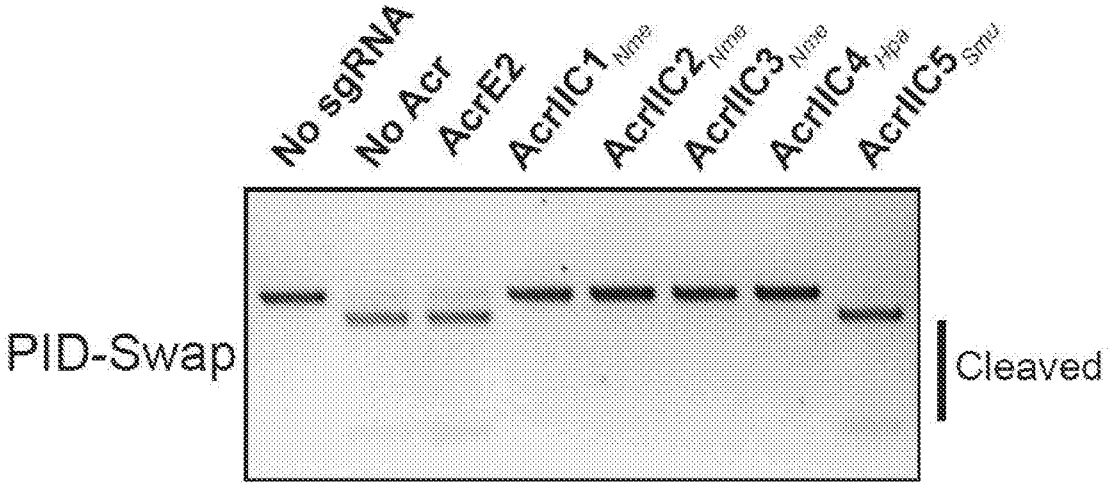

No sgRNA
No Acr
AcrE2
AcrIIC1 Nme
AcrIIC2 Nme
AcrIIC3 Nme
AcrIIC4 Hpa
AcrIIC5 Smu
PID-Swap
Cleaved

Figure 41

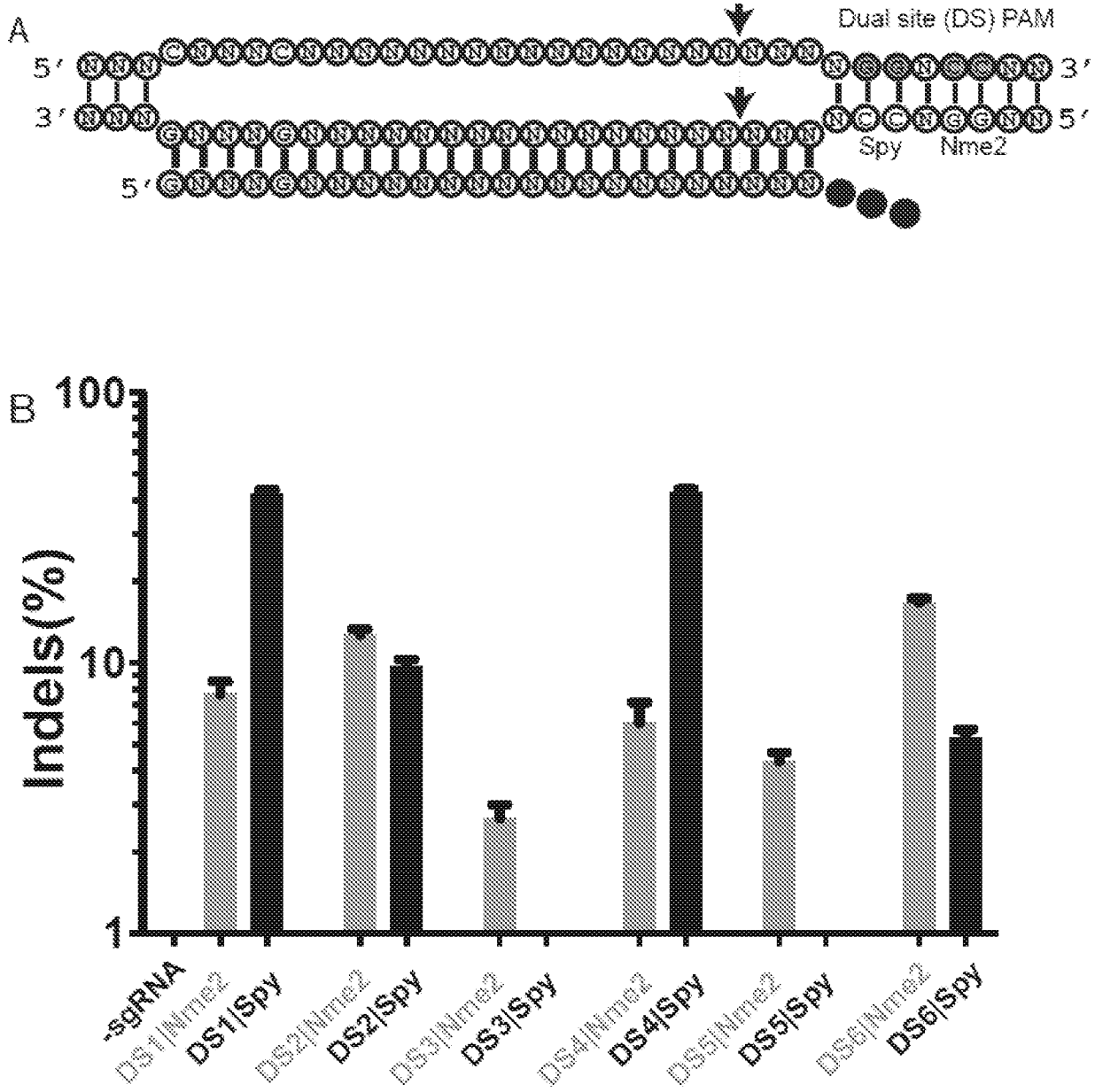

A
Dual site (DS) PAM
5′
3′
Spy
Nme2
B
100
10
1
Indels(%)
-sgRNA
DS1|Nme2
DS1|Spy
DS2|Nme2
DS2|Spy
DS3|Nme2
DS3|Spy
DS4|Nme2
DS4|Spy
DS5|Nme2
DS5|Spy
DS6|Nme2
DS6|Spy

Figure 42

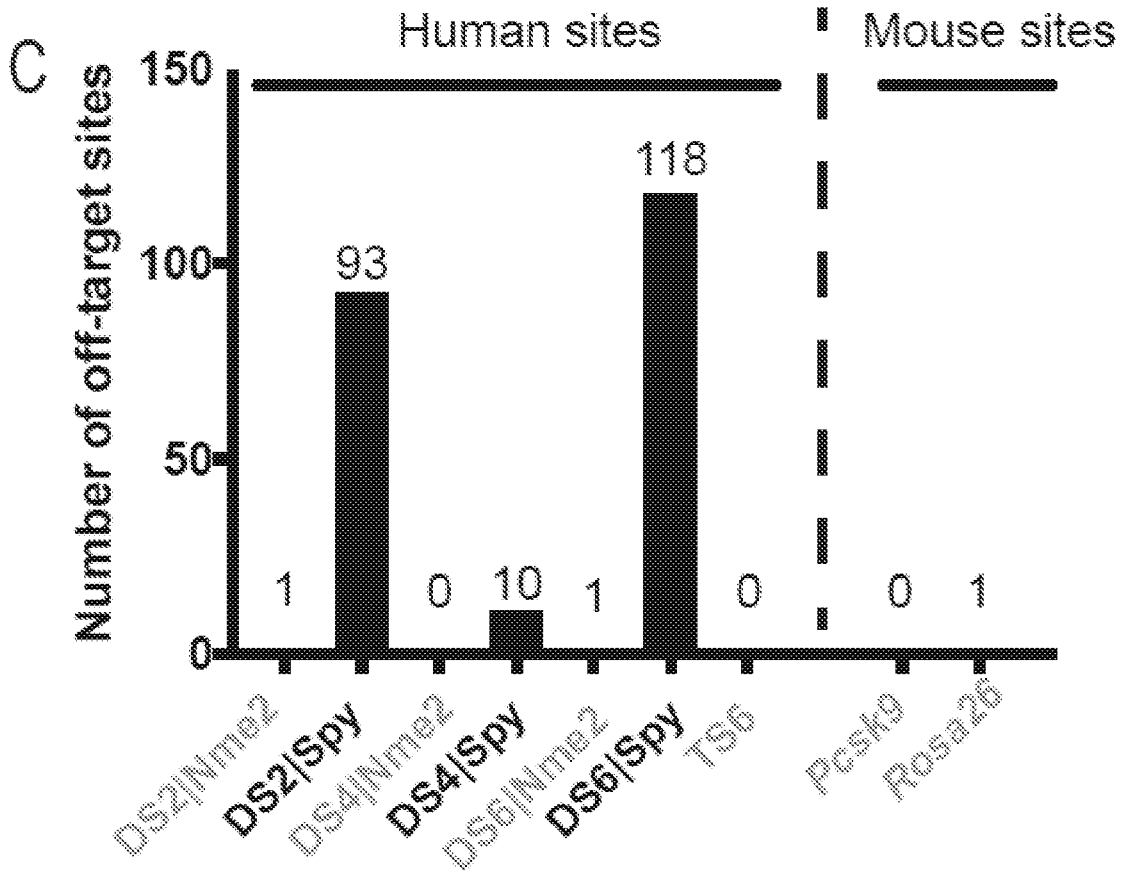


Figure 42 (cont'd)

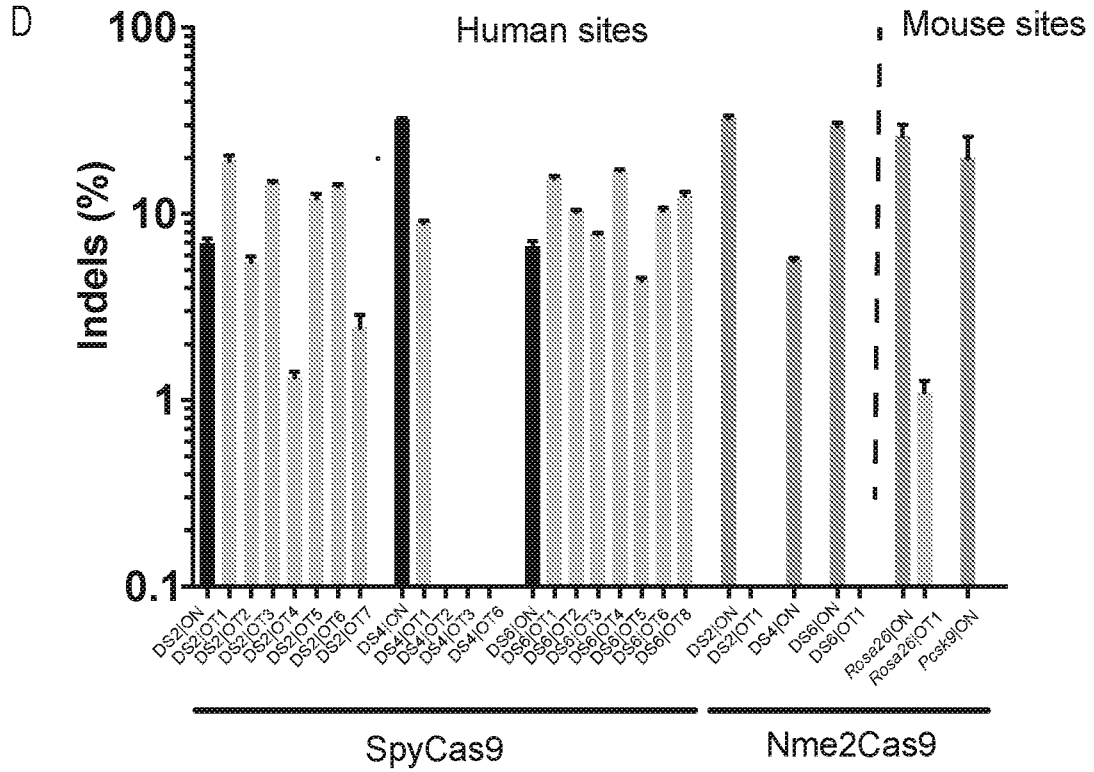


Figure 42 (cont'd)

Figure 42E

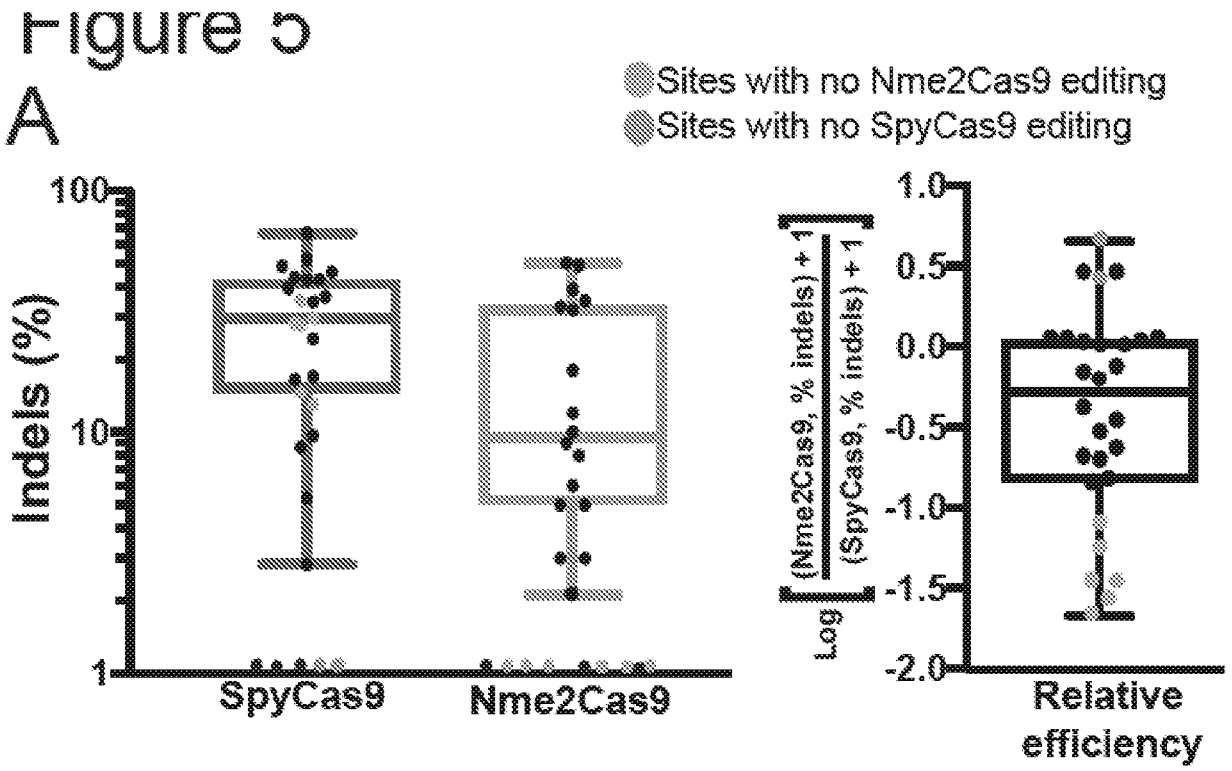


Figure 42F

Rosa26|On : TGAGGACCGCCCTGGGCCTGGGAGAATCCCT
Rosa26|OT1 : GAAGGACCACCCTAGGCCTGGGAGACTCCCT

Figure 42 (cont'd)

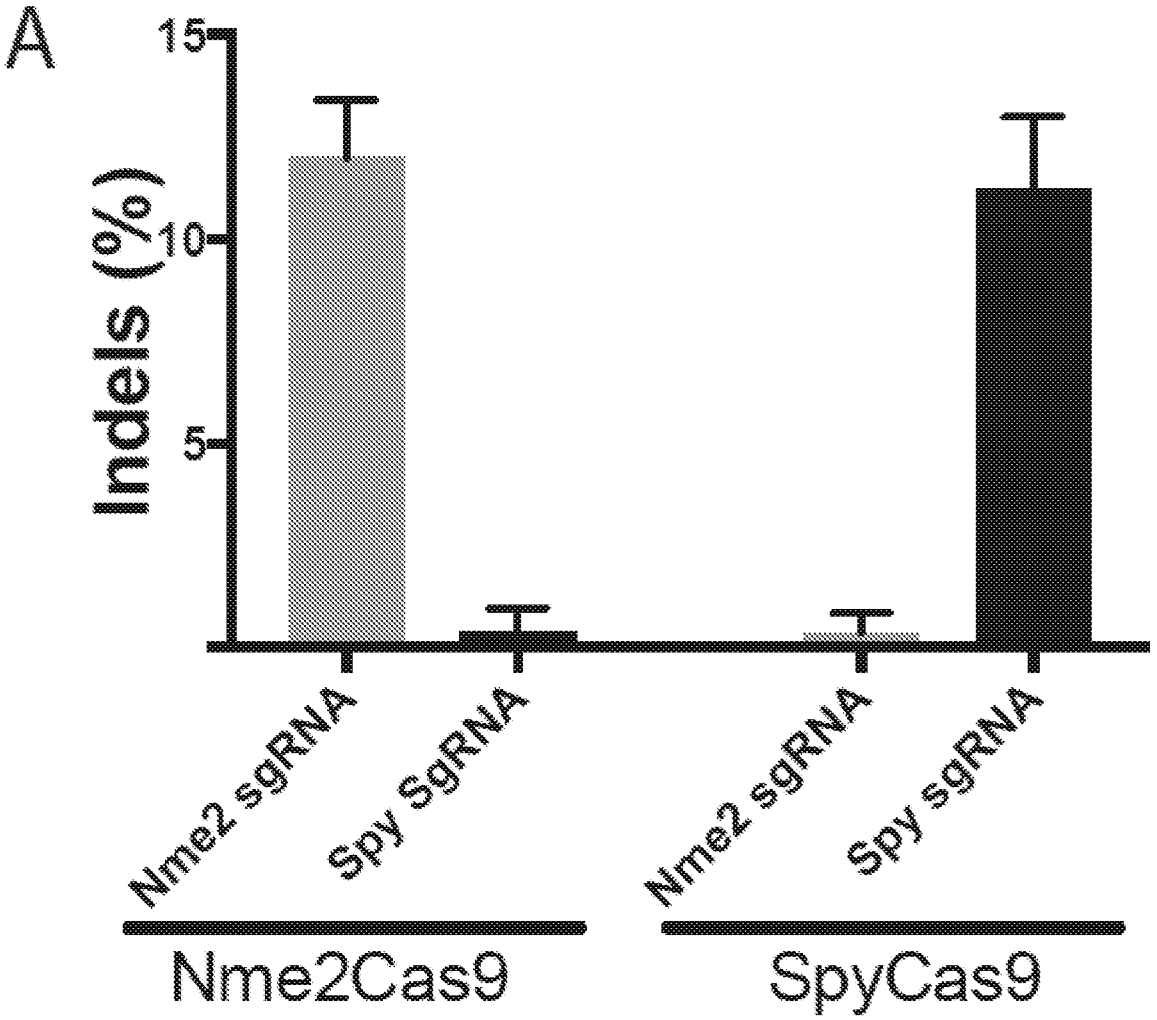

A
15
10
5
Indels (%)
Nme2 sgRNA
Spy sgRNA
Nme2 sgRNA
Spy sgRNA
Nme2Cas9
SpyCas9

Figure 43

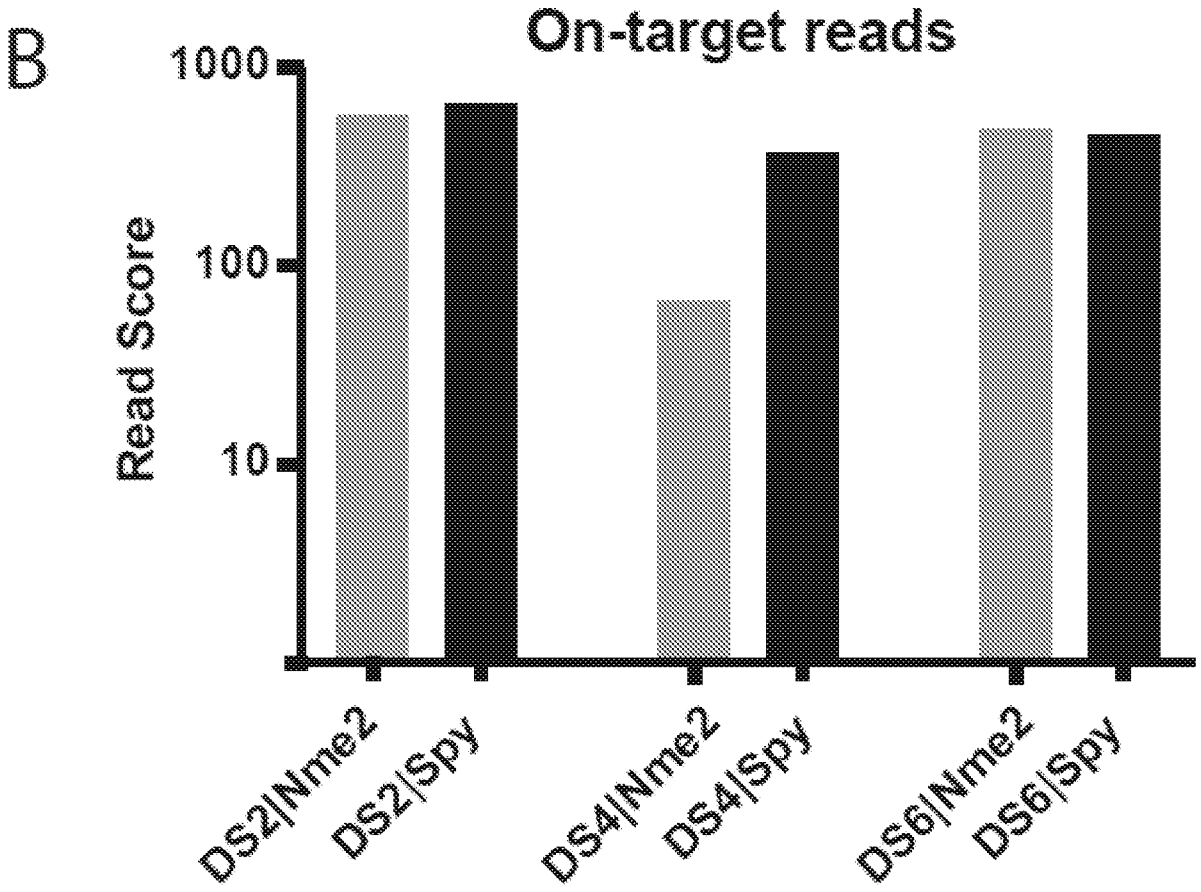


Figure 43 (cont'd)

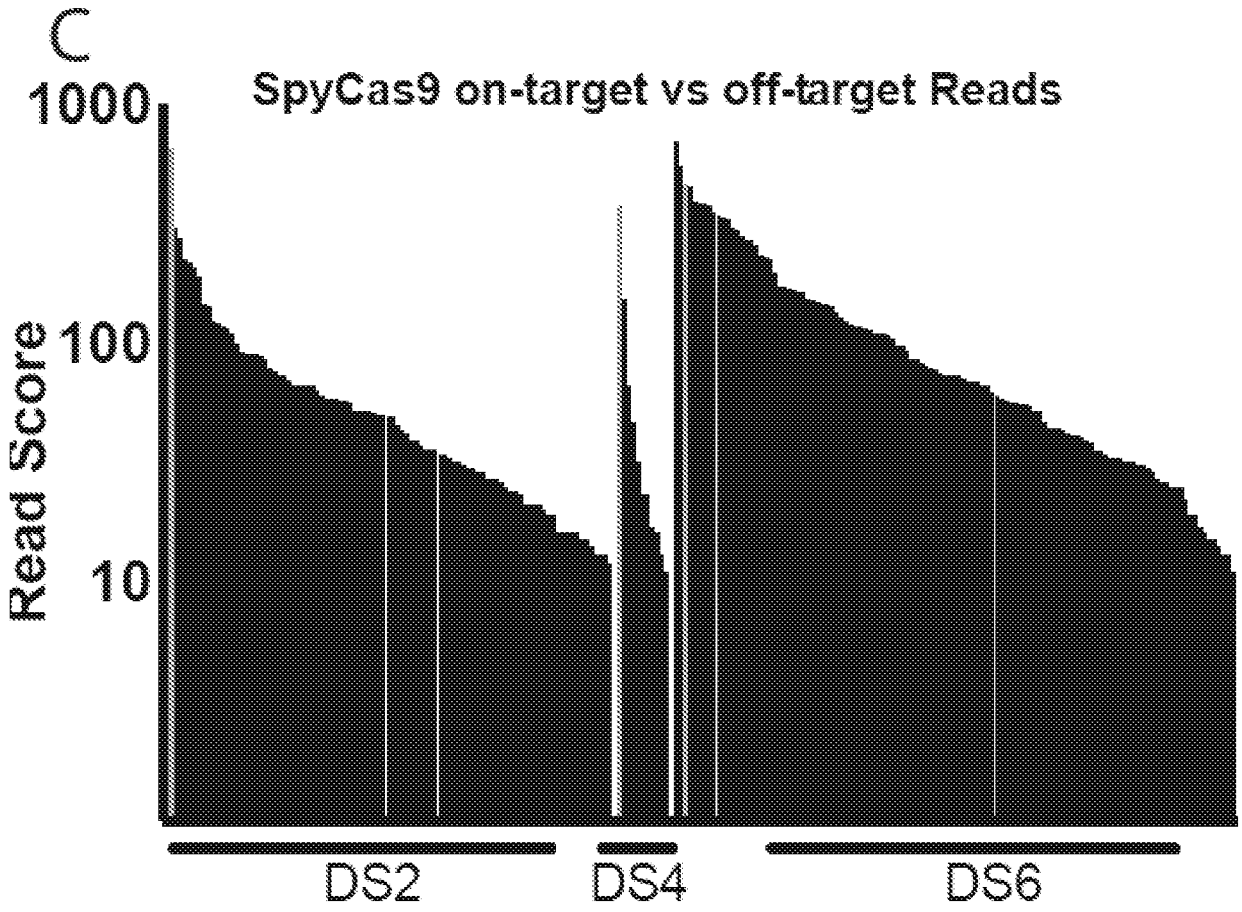


Figure 43 (cont'd)

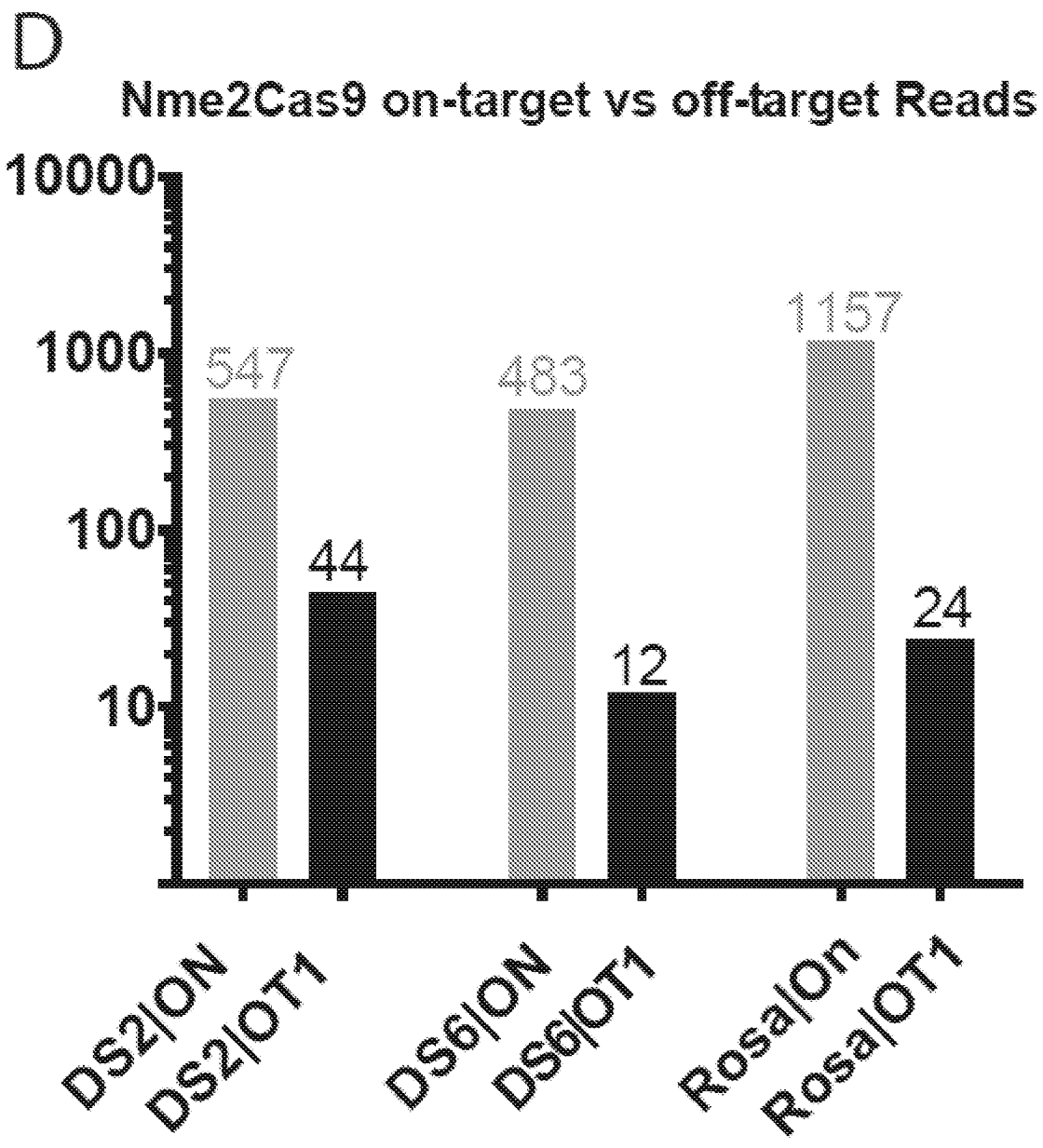


Figure 43 (cont'd)

E

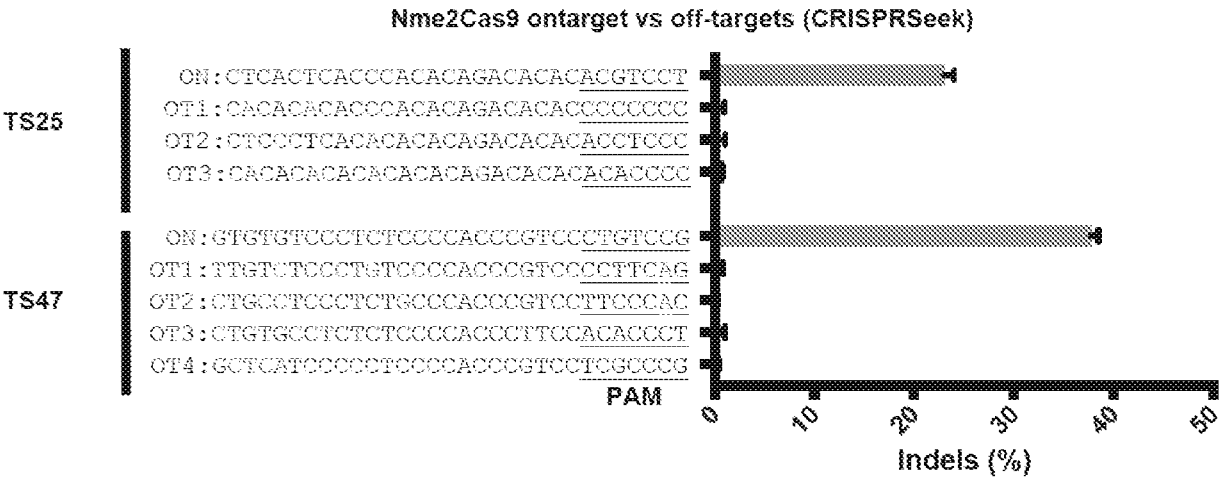
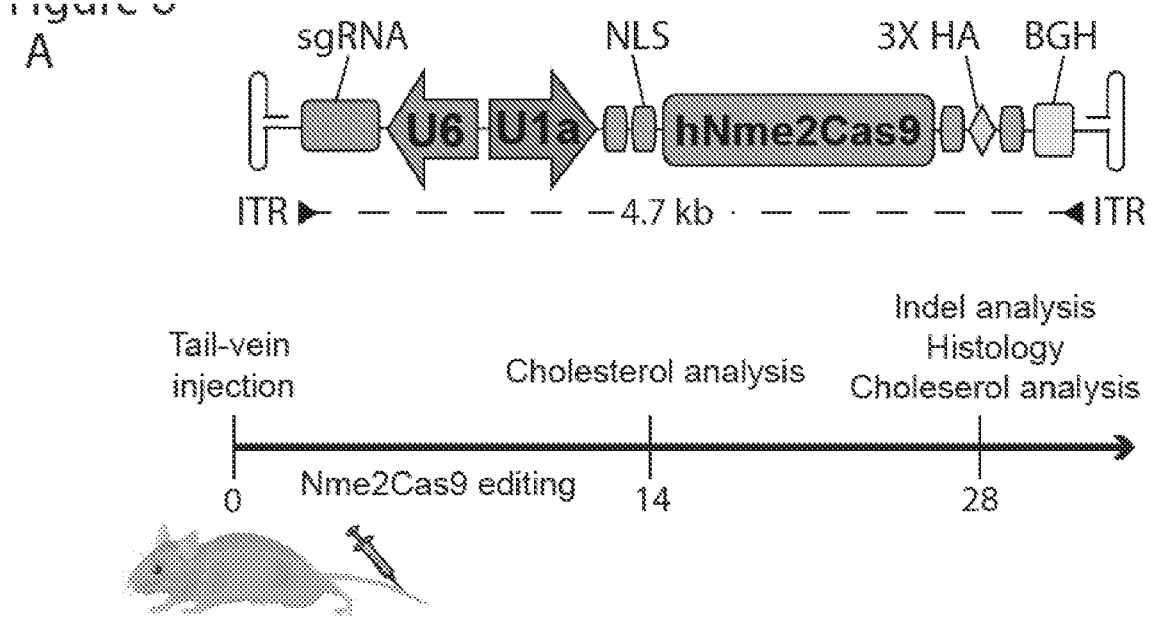


Figure 43 (cont'd)


A
sgRNA
NLS
3X HA
BGH
U6
U1a
hNme2Cas9
ITR
4.7 kb
ITR
Tail-vein injection
Cholesterol analysis
Indel analysis
Histology
Choleserol analysis
0
Nme2Cas9 editing
14
28

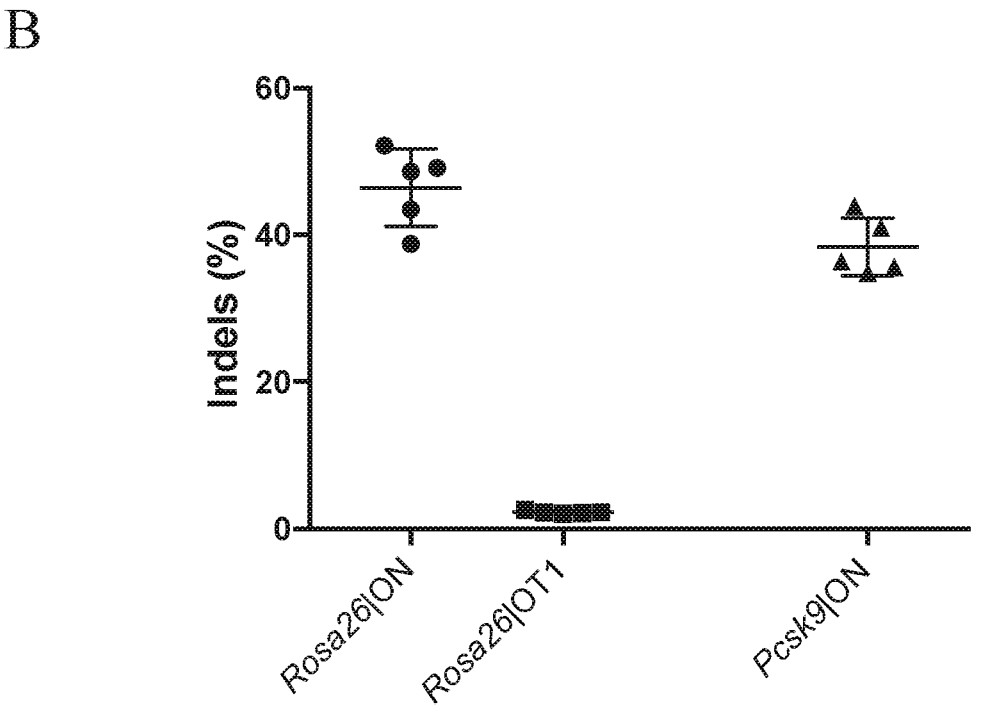
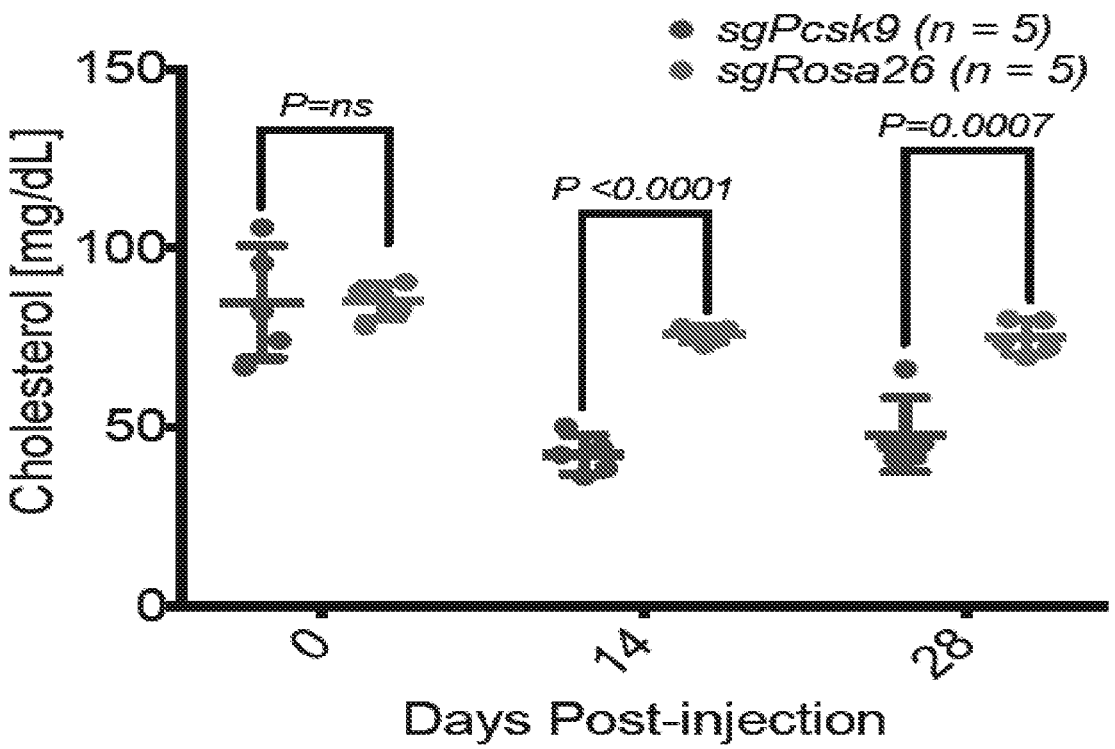

B
60
40
20
0
Indels (%)
Rosa26|ON
Rosa26|OT1
Pcsk9|ON

Figure 44

C



D

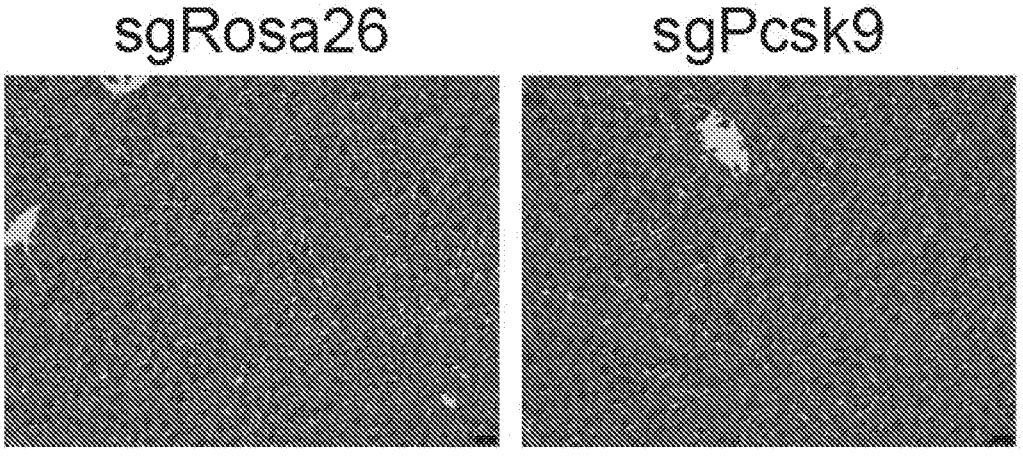


Figure 44 (cont'd)

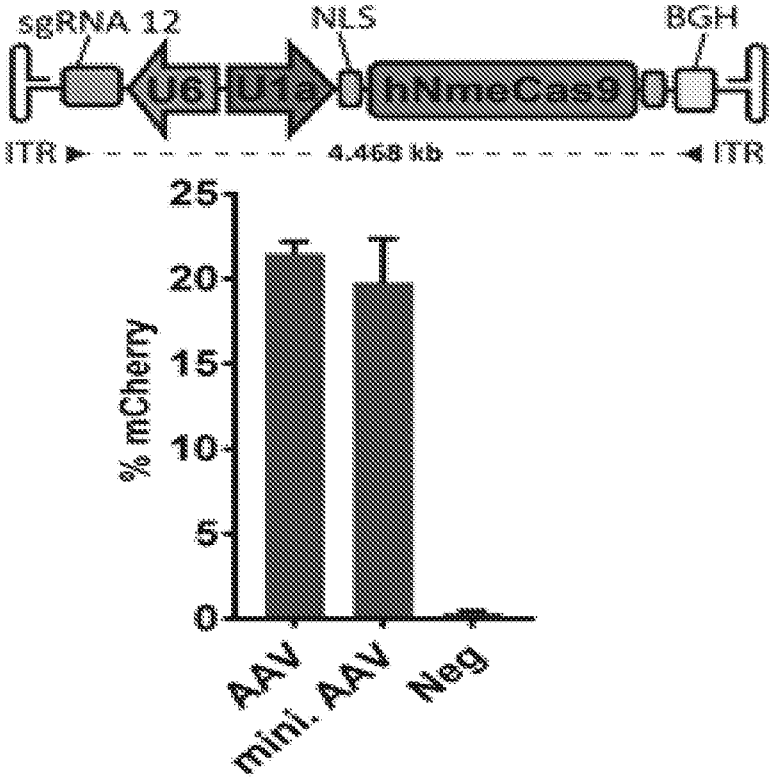

sgRNA 12
NLS
BGH
U6
hNmeCas9
ITR
4.468 kb
ITR
% mCherry
25
20
15
10
5
0
AAV
mini. AAV
Neg

Figure 45

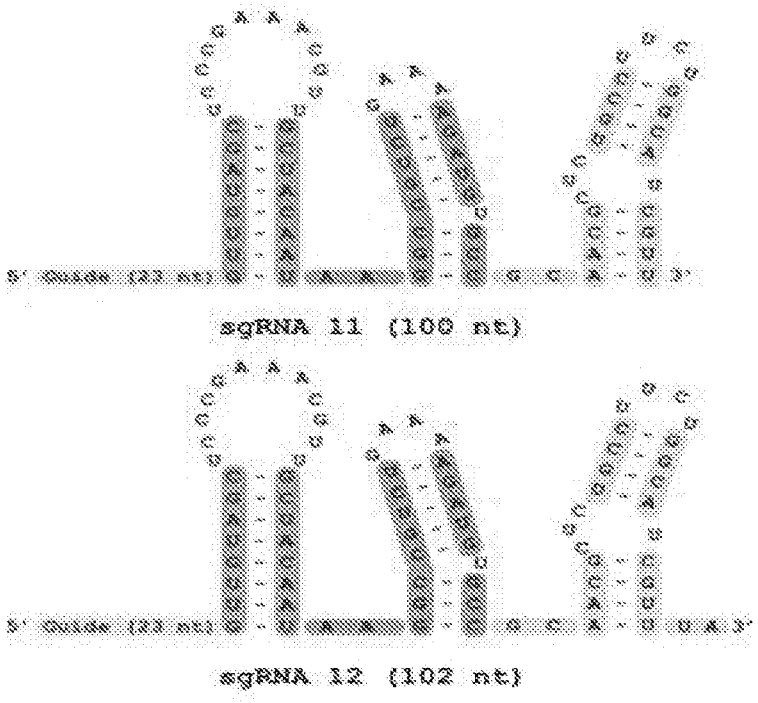


Figure 46

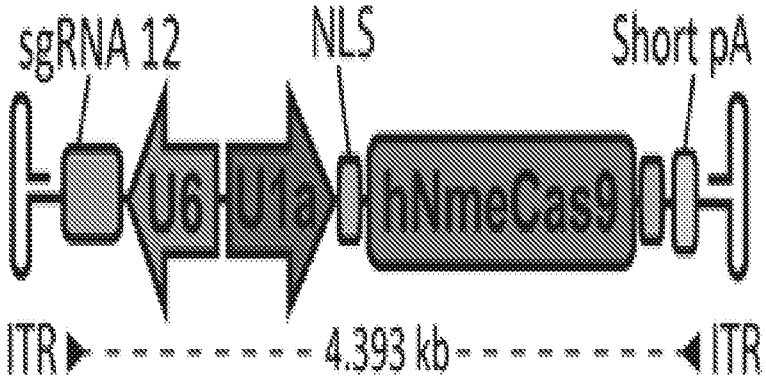
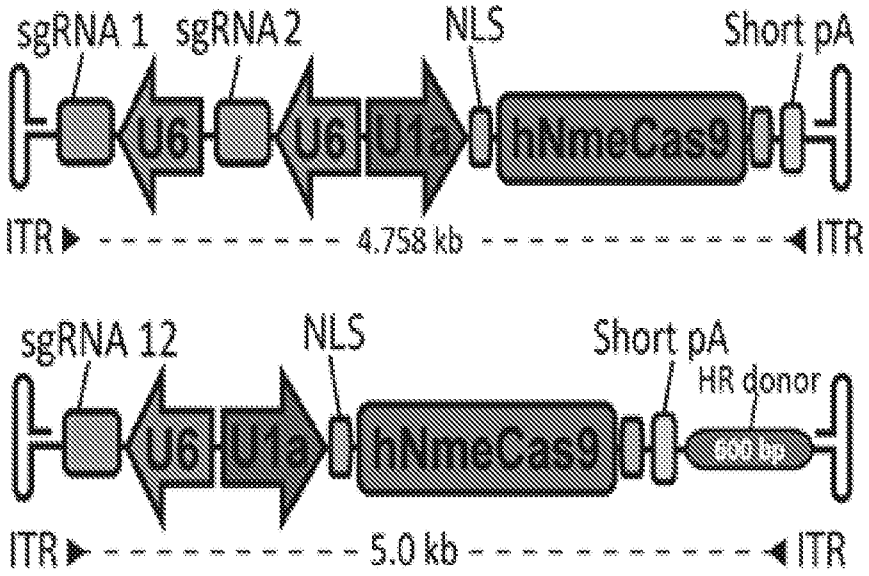


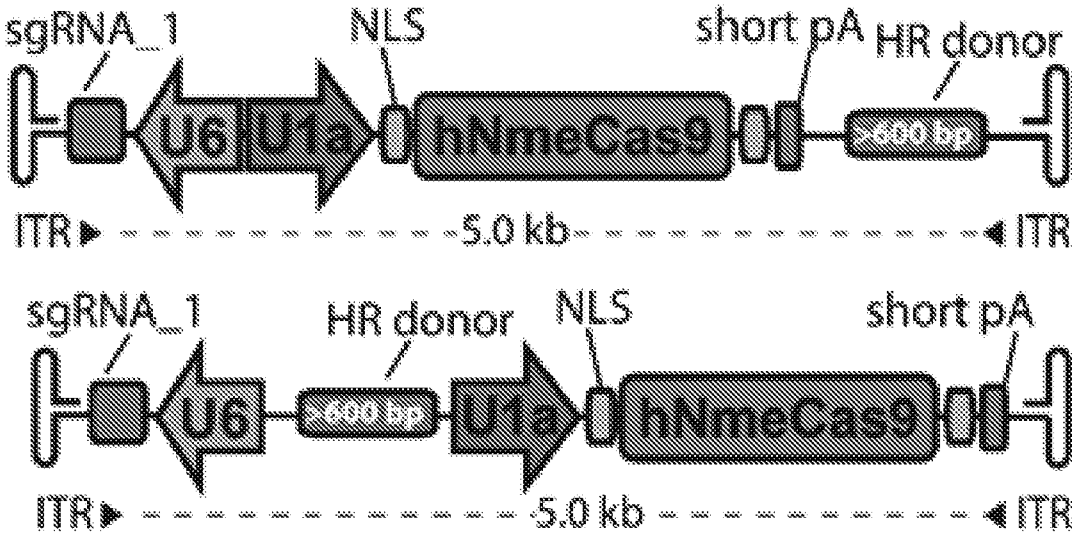
Figure 47

A



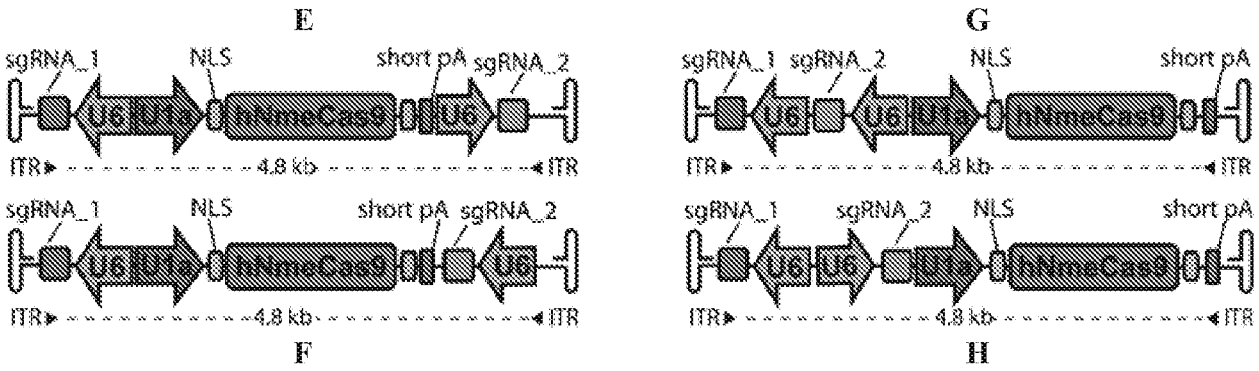
B

C

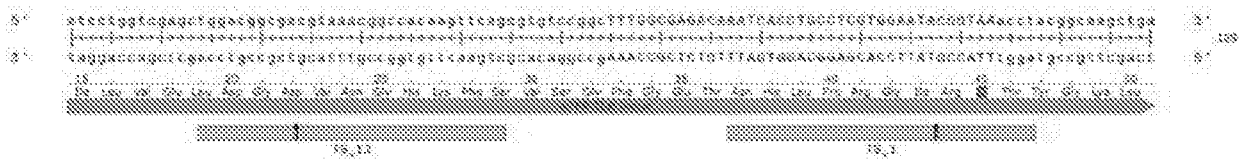


D

Figure 48



I



J

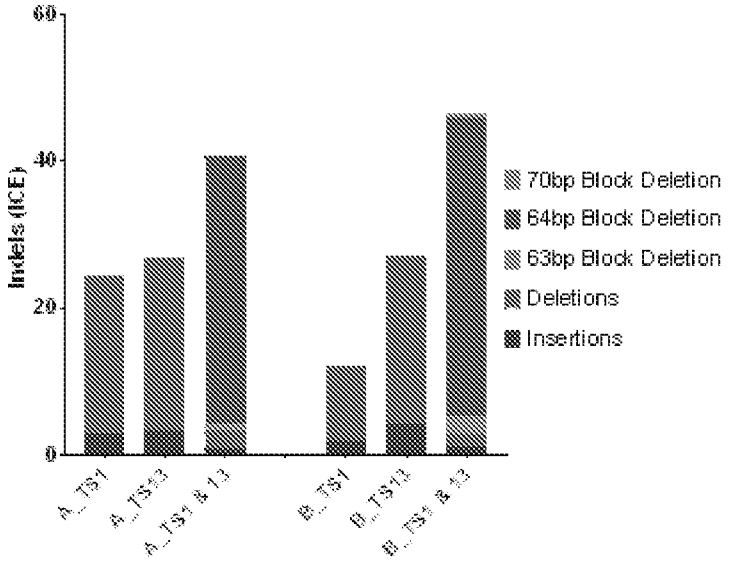


Figure 48 (cont'd)

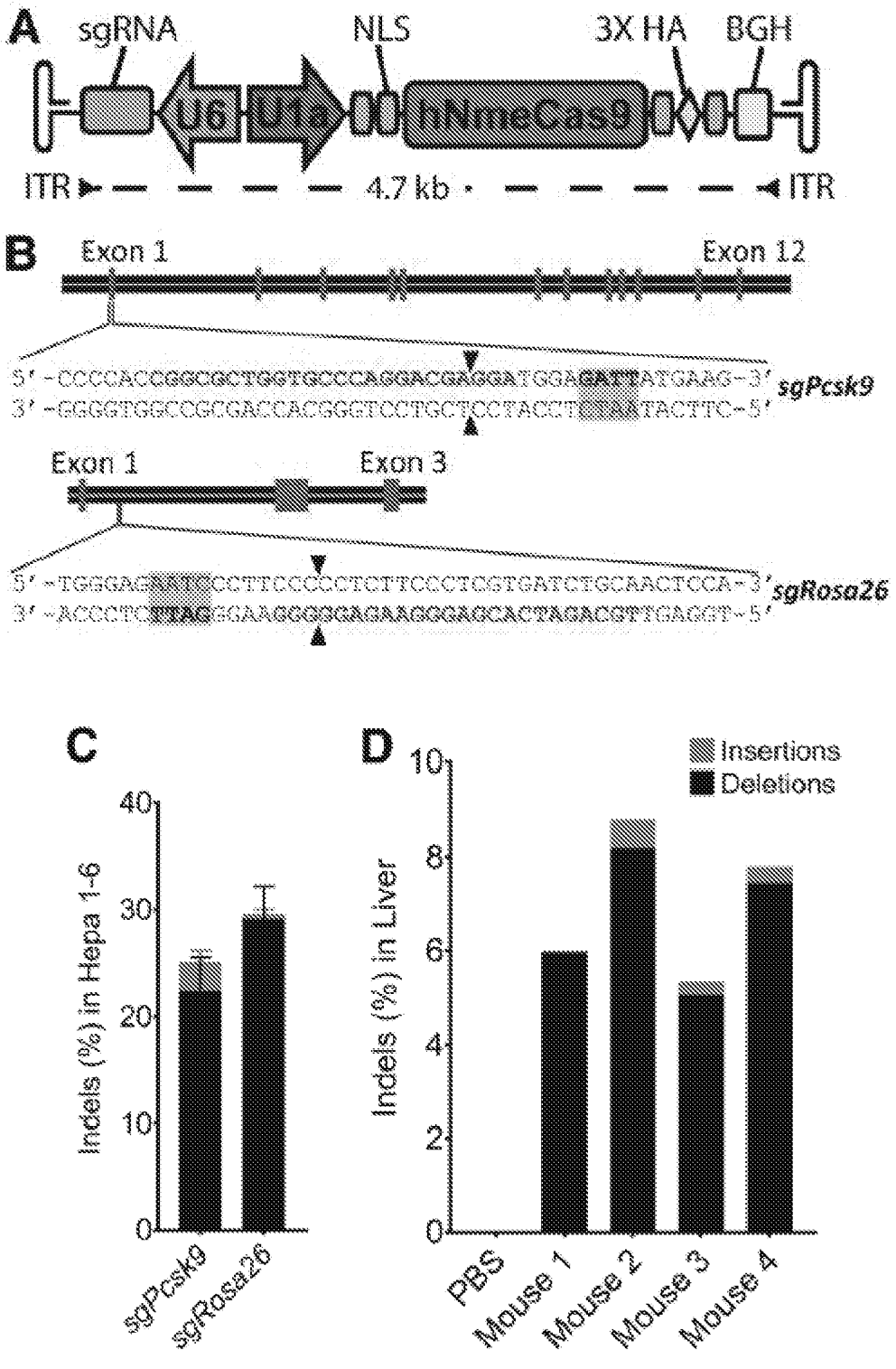

A
sgRNA
NLS
3X HA
BGH
U6
U1a
hNmeCas9
ITR
4.7 kb
ITR
B
Exon 1
Exon 12
sgPcsk9
Exon 1
Exon 3
sgRosa26
C
Indels (%) in Hepa 1-6
sgPcsk9
sgRosa26
D
Insertions
Deletions
Indels (%) in Liver
PBS
Mouse 1
Mouse 2
Mouse 3
Mouse 4

Figure 49

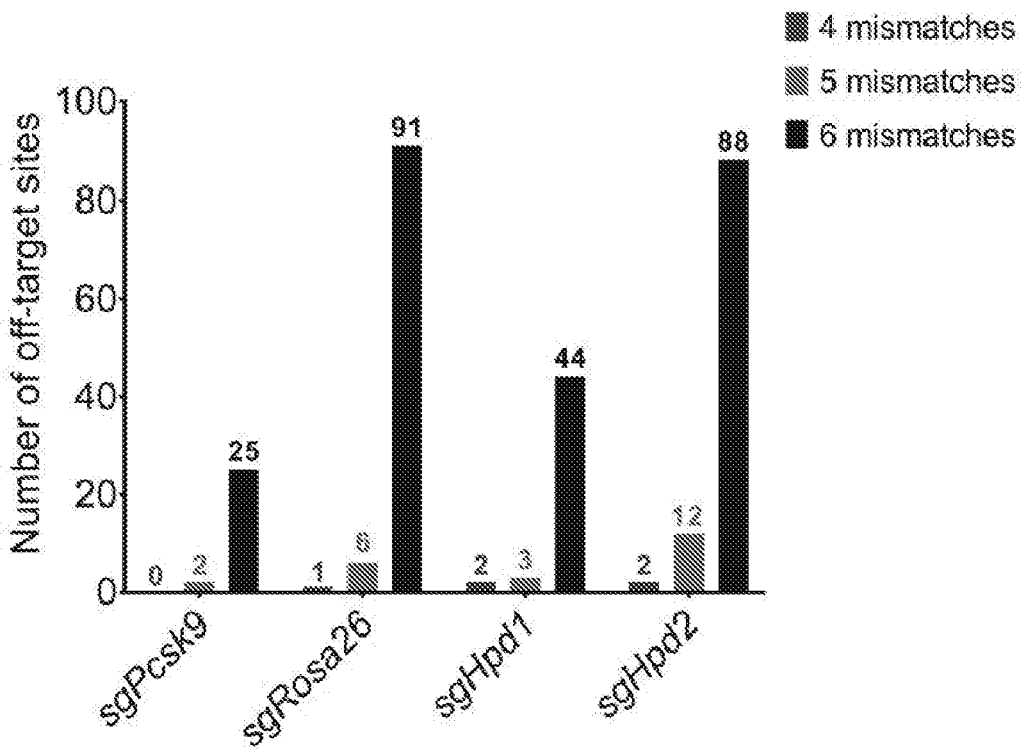

4 mismatches
5 mismatches
6 mismatches
Number of off-target sites
100
80
60
40
20
0
0
2
25
1
6
91
2
3
44
2
12
88
sgPcsk9
sgRosa26
sgHpd1
sgHpd2

Figure 50

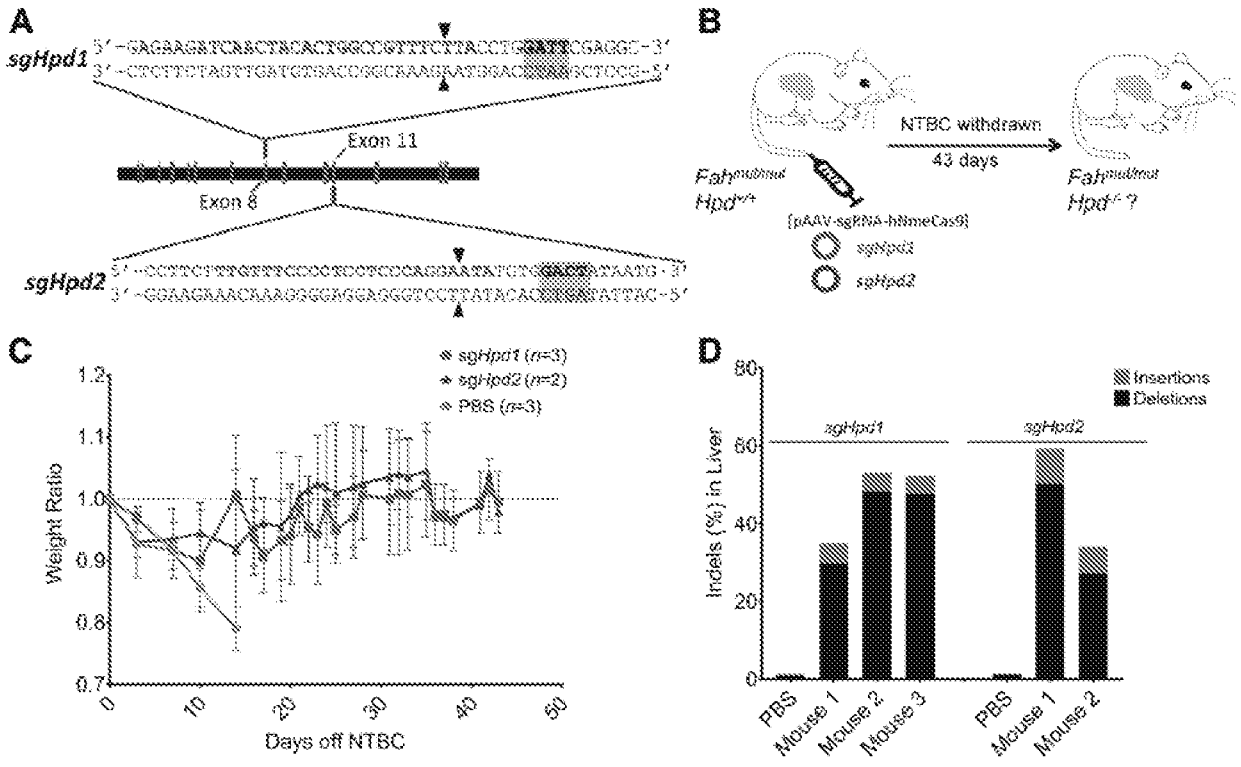

A
sgHpd1
Exon 11
Exon 6
sgHpd2
B
NTBC withdrawn
43 days
Fah mut/mut
Hpd +/+
Fah mut/mut
Hpd -/-?
(pAAV-sgRNA-hSmeCas9)
sgHpd1
sgHpd2
C
sgHpd1 (n=3)
sgHpd2 (n=2)
PBS (n=3)
Weight Ratio
Days off NTBC
D
Insertions
Deletions
sgHpd1
sgHpd2
Indels (%) in Liver
PBS
Mouse 1
Mouse 2
Mouse 3
PBS
Mouse 1
Mouse 2

Figure 51

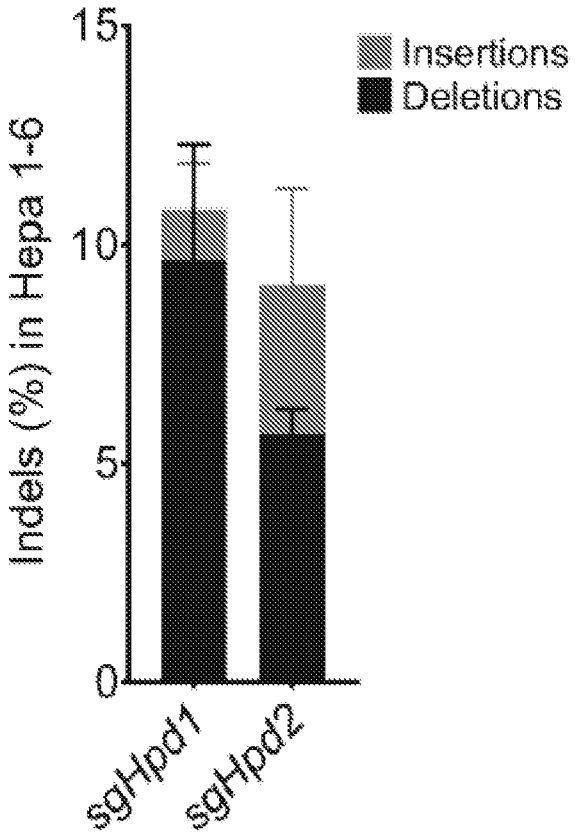

15
10
5
0
Indels (%) in Hepa 1-6
Insertions
Deletions
sgHpd1
sgHpd2

Figure 52

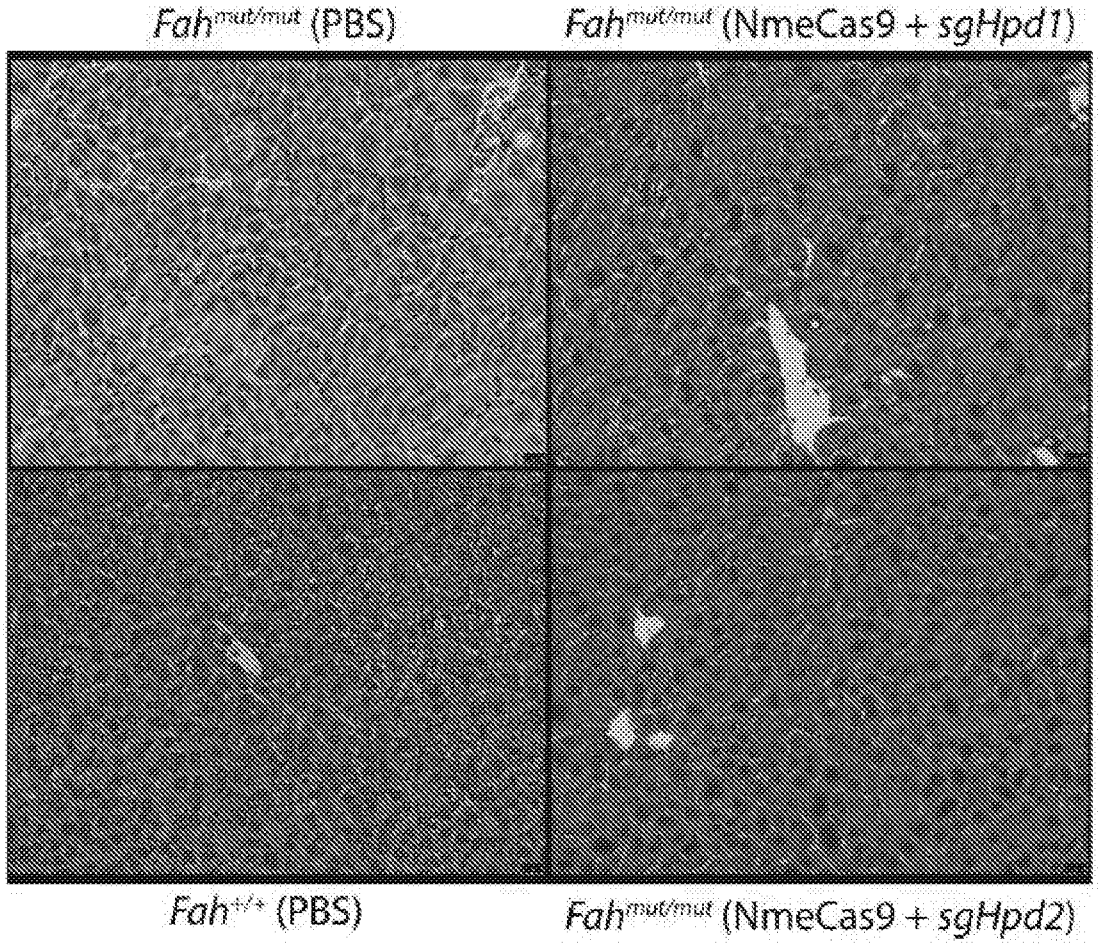

Fah^mut/mut (PBS)
Fah^mut/mut (NmeCas9 + sgHpd1)
Fah^+/+ (PBS)
Fah^mut/mut (NmeCas9 + sgHpd2)

Figure 53

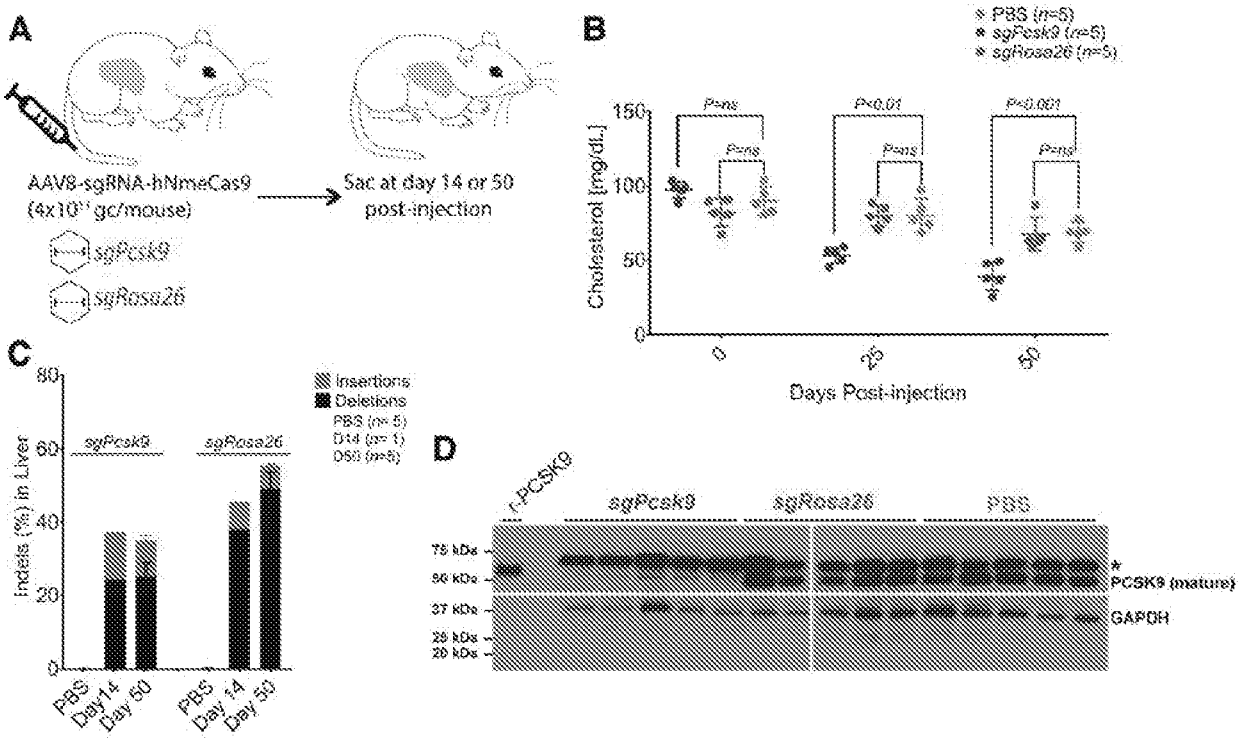
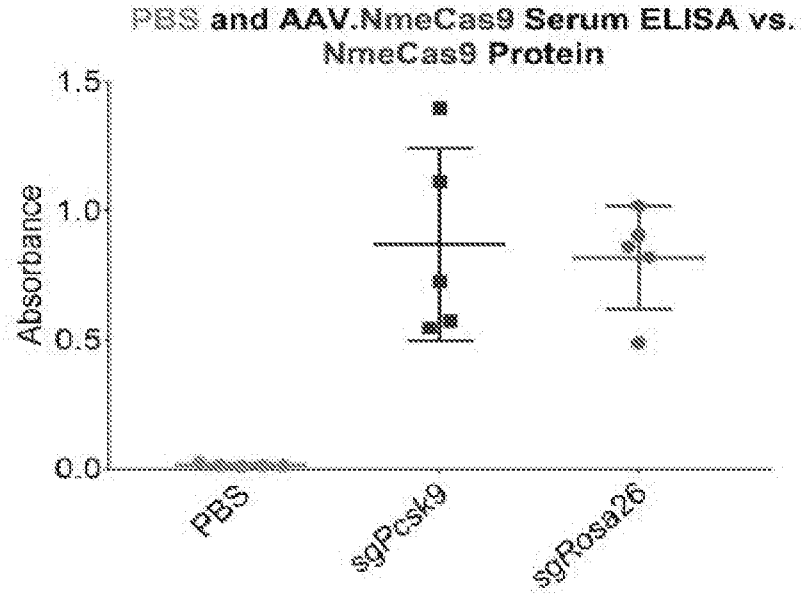

A
AAV8-sgRNA-hNmeCas9
(4x10^11 gc/mouse)
Sac at day 14 or 50
post-injection
sgPcsk9
sgRosa26
B
PBS (n=5)
sgPcsk9 (n=5)
sgRosa26 (n=5)
Cholesterol (mg/dL)
Days Post-injection
C
Insertions
Deletions
PBS (n= 5)
D14 (n= 1)
D50 (n=5)
Indels (%) in Liver
sgPcsk9
sgRosa26
PBS
Day14
Day 50
D
r-PCSK9
sgPcsk9
sgRosa26
PBS
75 kDa
50 kDa
37 kDa
25 kDa
20 kDa
PCSK9 (mature)
GAPDH

Figure 54

A


PBS and AAV.NmeCas9 Serum ELISA vs. NmeCas9 Protein
Absorbance
1.5
1.0
0.5
0.0
PBS
sgPcsk9
sgRosa26

B

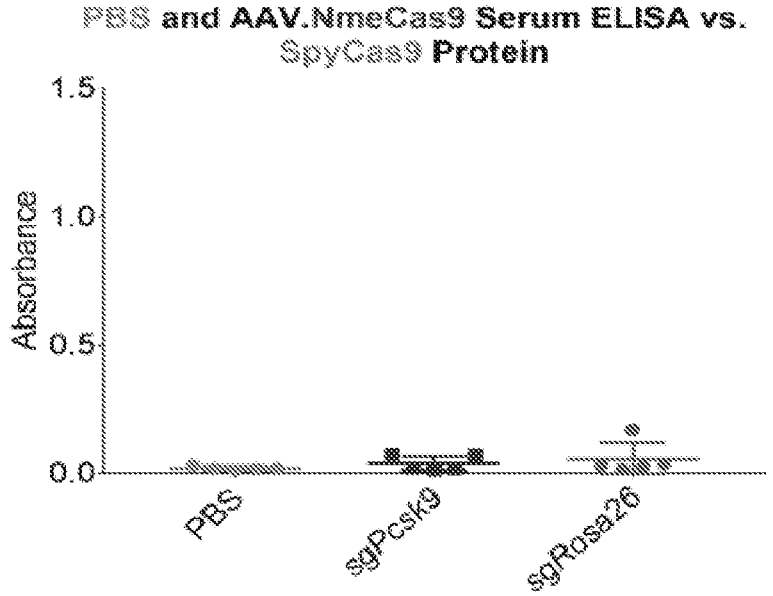

PBS and AAV.NmeCas9 Serum ELISA vs. SpyCas9 Protein
Absorbance
1.5
1.0
0.5
0.0
PBS
sgPcsk9
sgRosa26

Figure 55

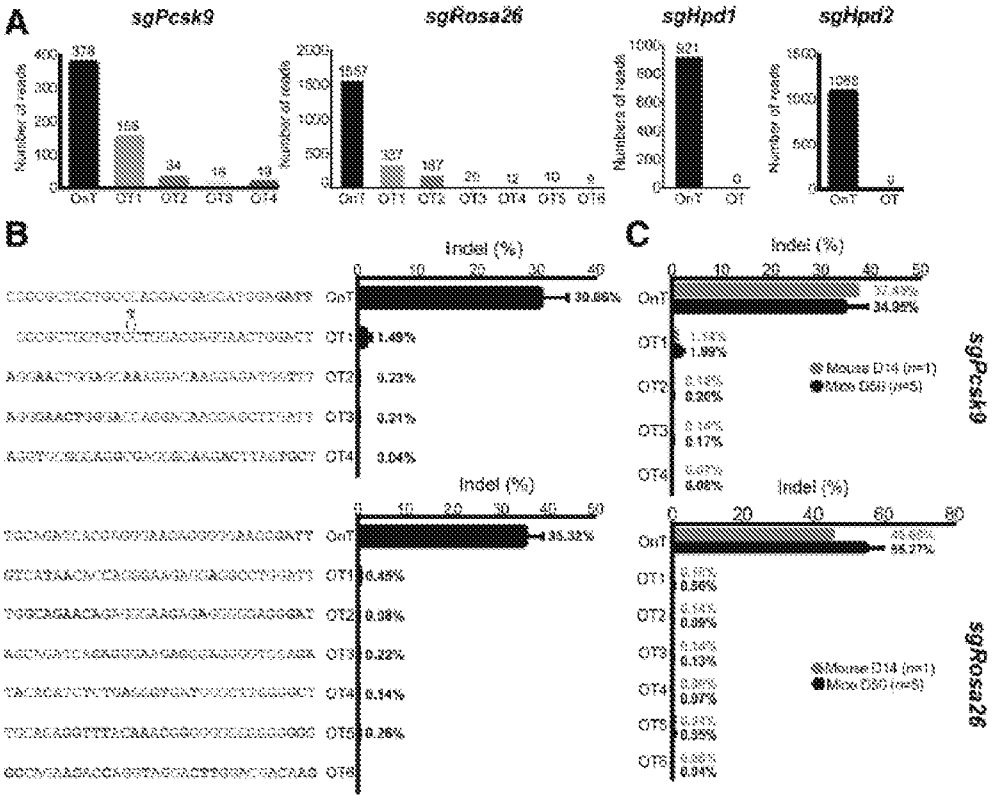
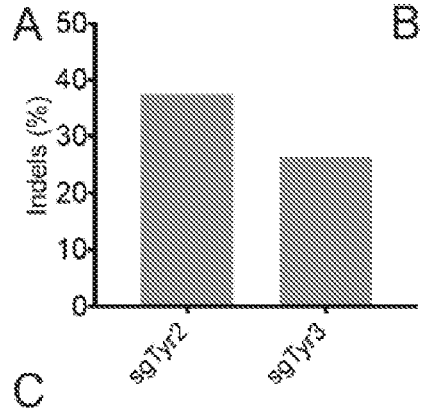

A
sgPcsk9
sgRosa26
sgHpd1
sgHpd2
Number of reads
On-T
OT1
OT2
OT3
OT4
OT5
OT6
B
Indel (%)
39.68%
1.49%
9.23%
9.21%
3.04%
35.32%
0.46%
0.38%
0.32%
0.14%
0.26%
C
Indel (%)
36.82%
1.99%
0.26%
0.17%
0.08%
98.27%
0.56%
0.38%
0.13%
0.97%
0.35%
0.04%
Mouse D14 (n=1)
Mice D60 (n=5)
Mice D60 (n=3)
sgPcsk9
sgRosa26

Figure 56



B

Mouse ID	AAV dosage	Indels (%)	Coat color
9-1	3 x 10^9 GCs	100	Albino
9-2	3 x 10^9 GCs	100	Albino
9-3	3 x 10^9 GCs	84	mosaic and hypomorphic
9-4	3 x 10^9 GCs	98	mosaic and hypomorphic
9-5	3 x 10^9 GCs	100	mosaic and hypomorphic
8-1	3 x 10^8 GCs	100	mosaic and hypomorphic
8-2	3 x 10^8 GCs	96	mosaic and hypomorphic

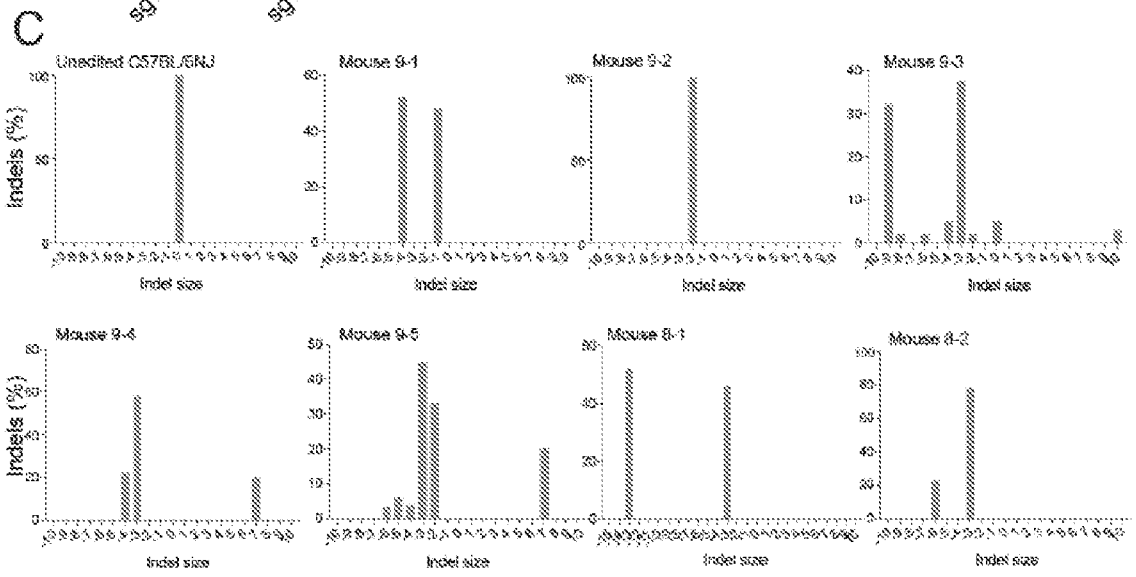
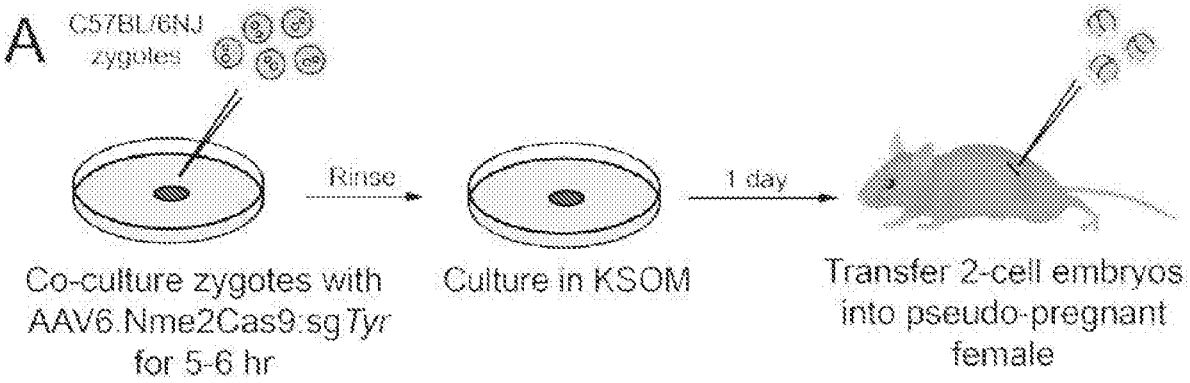
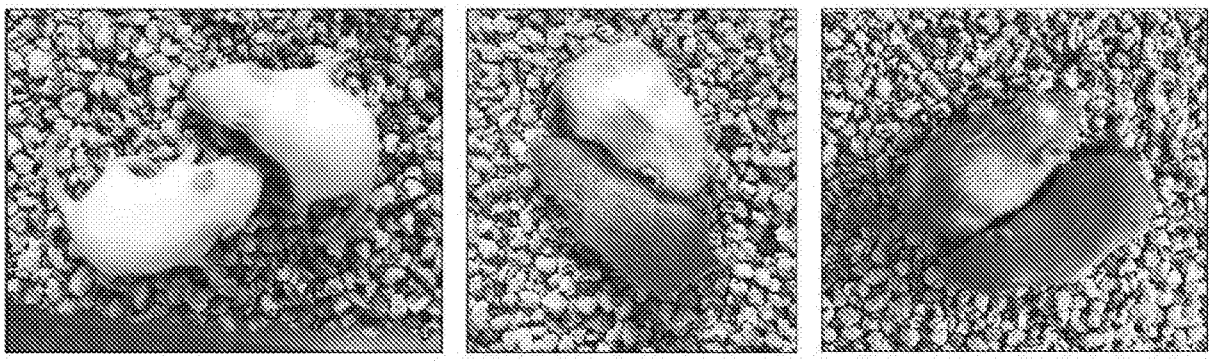


Figure 57

A



B



C

AAV Dosage	Number of embryos transferred	Number of pups recovered	Number of *Tyr*-edited pups (albino or chinchilla)	*Tyr* editing frequency (%)
3 x 10^6 GCs	50	5	5 (3)	100
3 x 10^5 GCs	28	2*	2 (1)	100

Figure 58

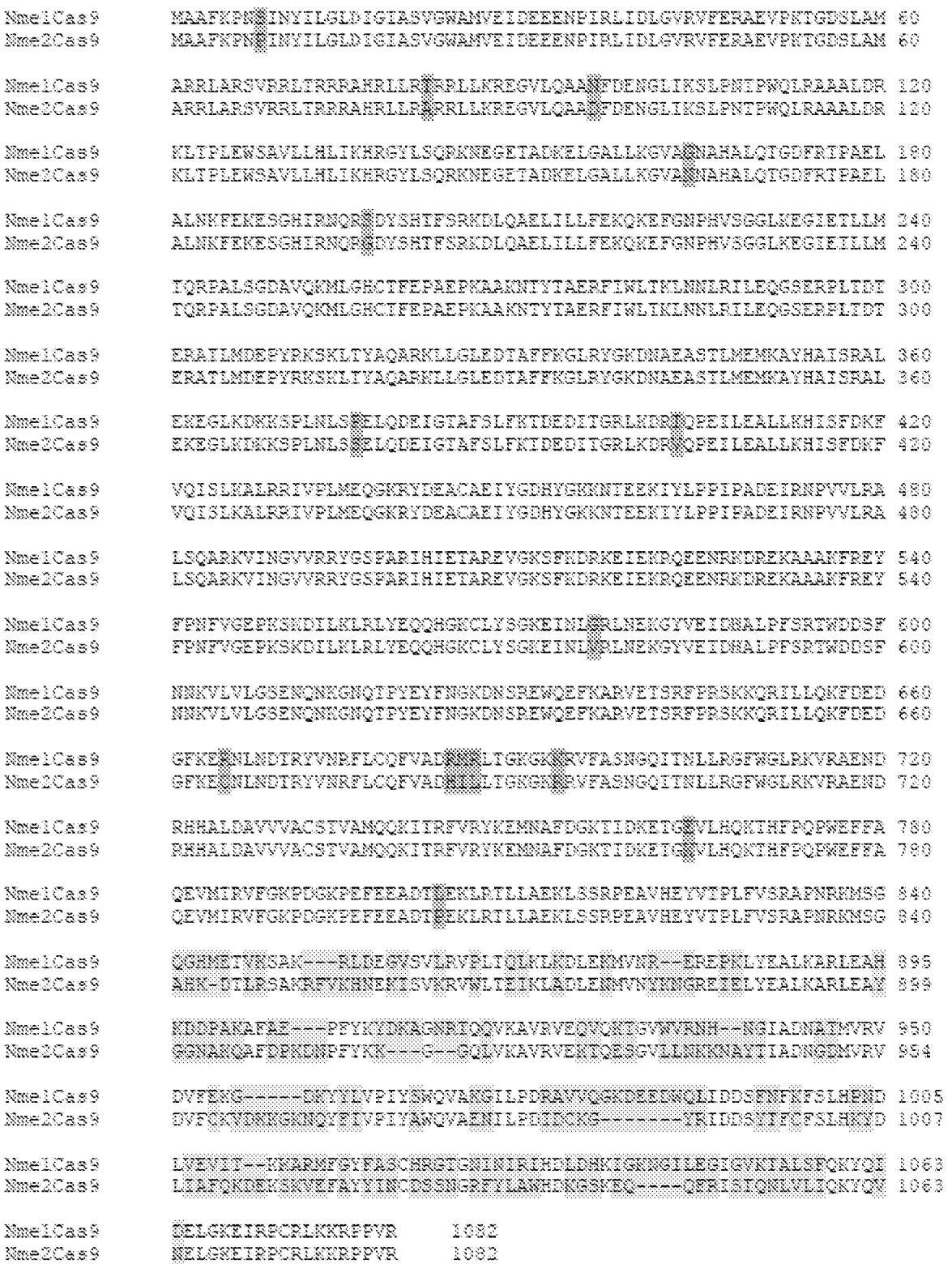


Figure 59



Figure 60

MAAFKPNPINYILGLDIGIASVGWAMVEIDEEENPIRLIDLGVRVFERAEVPKTGDSLA
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AALDRKLTPLEWSAVLLHLIKHRGYLSQRKNEGETADKELGALLKGVANNAHALQT
GDFRTPAELALNKFEKESGHIRNQRGDYSHTFSRKDLQAELILLFEKQKEFGNPHVS
GGLKEGIETLLMTQRPALSGDAVQKMLGHCTFEPAEPKAAKNTYTAERFIWLTKLN
NLRILEQGSERPLTDTERATLMDEPYRKSKLTYAQARKLLGLEDTAFFKGLRYGKDN
AEASTLMEMKAYHAISRALEKEGLKDKKSPLNLSSELQDEIGTAFSLFKTDEDITGRL
KDRVQPEILEALLKHISFDKFVQISLKALRRIVPLMEQGKRYDEACAEIYGDHYGKKN
TEEKIYLPPIPADEIRNPVVLRALSQARKVINGVVRRYGSPARIHIETAREVGKSFKDR
KEIEKRQEENRKDREKAAAKFREYFPNFVGEPKSKDILKLRLYEQQHGKCLYSGKEI
NLVRLNEKGYVEIDHALPFSRTWDDSFNNKVLVLGSENQNKGNQTPYEYFNGKDNS
REWQEFKARVETSRFPRSKKQRILLQKFDEDGFKECNLNDTRYVNRFLCQFVADHIL
LTGKGKRRVFASNGQITNLLRGFWGLRKVRAENDRHHALDAVVVACSTVAMQQKI
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EEADTPEKLRTLLAEKLSSRPEAVHEYVTPLFVSRAPNRKMSGAHKDTLRSAKRFVK
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DNPFYKKGGQLVKAVRVEKTQESGVLLNKKNAYTIADNGDMVRVDVFCKVDKKG
KNQYFIVPIYAWQVAENILPDIDCKGYRIDDSYTFCFSLHKYDLIAFQKDEKSKVEFAY
YINCDSSNGRFYLAWHDKGSKEQQFRISTQNLVLIQKYQVNELGKEIRPCRLKKRPP
VRSDVAQPKKKRKVYYYDVIDYAGYPYDVPDYAGSYPYDVPDYAGSAAPAAKKKKL
DFESG*

Figure 61

MVPKKKRKV[illegible]MAAFKPNPINYILGLDIGIASVGWAMVEI
DEEENPIRLIDLGVRVFERAEVPKTGDSLAMARRLARSVRRLTRRRAHRLLRARRLL
KREGVLQAADFDENGLIKSLPNTPWQLRAAALDRKLTPLEWSAVLLHLIKHRGYLSQ
RKNEGETADKELGALLKGVANNAHALQTGDFRTPAELALNKFEKESGHIRNQRGDY
SHTFSRKDLQAELILLFEKQKEFGNPHVSGGLKEGIETLLMTQRPALSGDAVQKMLG
HCTFEPAEPKAAKNTYTAERFIWLTKLNNLRILEQGSERPLTDTERATLMDEPYRKS
KLTYAQARKLLGLEDTAFFKGLRYGKDNAEASTLMEMKAYHAISRALEKEGLKDKK
SPLNLSSELQDEIGTAFSLFKTDEDITGRLKDRVQPEILEALLKHISFDKFVQISLKALR
RIVPLMEQGKRYDEACAEIYGDHYGKKNTEEKIYLPPIPADEIRNPVVLRALSQARKV
INGVVRRYGSPARIHIETAREVGKSFKDRKEIEKRQEENRKDREKAAAKFREYFPNFV
GEPKSKDILKLRLYEQQHGKCLYSGKEINLVRLNEKGYVEIDHALPFSRTWDDSFNN
KVLVLGSENQNKGNQTPYEYFNGKDNSREWQEFKARVETSRFPRSKKQRILLQKFD
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VRAENDRHHALDAVVVACSTVAMQQKITRFVRYKEMNAFDGKTIDKETGKVLHQ
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PLFVSRAPNRKMSGAHKDTLRSAKRFVKHNEKISVKRVWLTEIKLADLENMVNYKN
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DSYTFCFSLHKYDLIAFQKDEKSKVEFAYYINCDSSNGRFYLAWHDKGSKEQQFRIST
QNLVLIQKYQVNELGKEIRPCRLKKRPPVR[illegible]
[illegible]PAAKKKKLD*

Figure 62

PKKKRKV[redacted]MAAFKPNPINYILGLDIGIASVGWAMVEIDEEENPIRLIDLGVRVFERAE
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NTPWQLRAAALDRKLTPLEWSAVLLHLIKHRGYLSQRKNEGETADKELGALLKGVA
NNAHALQTGDFRTPAELALNKFEKESGHIRNQRGDYSHTFSRKDLQAELILLFEKQK
EFGNPHVSGGLKEGIETLLMTQRPALSGDAVQKMLGHCTFEPAEPKAAKNTYTAER
FIWLTKLNNLRILEQGSERPLTDTERATLMDEPYRKSKLTYAQARKLLGLEDTAFFK
GLRYGKDNAEASTLMEMKAYHAISRALEKEGLKDKKSPLNLSSELQDEIGTAFSLFKT
DEDITGRLKDRVQPEILEALLKHISFDKFVQISLKALRRIVPLMEQGKRYDEACAEIYG
DHYGKKNTEEKIYLPPIPADEIRNPVVLRALSQARKVINGVVRRYGSPARIHIETAREV
GKSFKDRKEIEKRQEENRKDREKAAAKFREYFPNFVGEPKSKDILKLRLYEQQHGK
CLYSGKEINLVRLNEKGYVEIDHALPFSRTWDDSFNNKVLVLGSENQNKGNQTPYEY
FNGKDNSREWQEFKARVETSRFPRSKKQRILLQKFDEDGFKECNLNDTRYVNRFLC
QFVADHILLTGKGKRRVFASNGQITNLLRGFWGLRKVRAENDRHHALDAVVVACS
TVAMQQKITRFVRYKEMNAFDGKTIDKETGKVLHQKTHFPQPWEFFAQEVMIRVF
GKPDGKPEFEEADTPEKLRTLLAEKLSSRPEAVHEYVTPLFVSRAPNRKMSGAHKDT
LRSAKRFVKHNEKISVKRVWLTEIKLADLENMVNYKNGREIELYEALKARLEAYGGN
AKQAFDPKDNPFYKKGGQLVKAVRVEKTQESGVLLNKKNAYTIADNGDMVRVDVF
CKVDKKGKNQYFIVPIYAWQVAENILPDIDCKGYRIDDSYTFCFSLHKYDLIAFQKDE
KSKVEFAYYINCDSSNGRFYLAWHDKGSKEQQFRISTQNLVLIQKYQVNELGKEIRP
CRLKKRPPVR[redacted]PAAKKKKLD[redacted]
*

Figure 63

gtttaaacaaaaaaatataaacgatgccccttaaagcagaagcttaaggggcagagcgttgcggcacatcttttcagacggccttattgtagcaacggttctc
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Figure 64