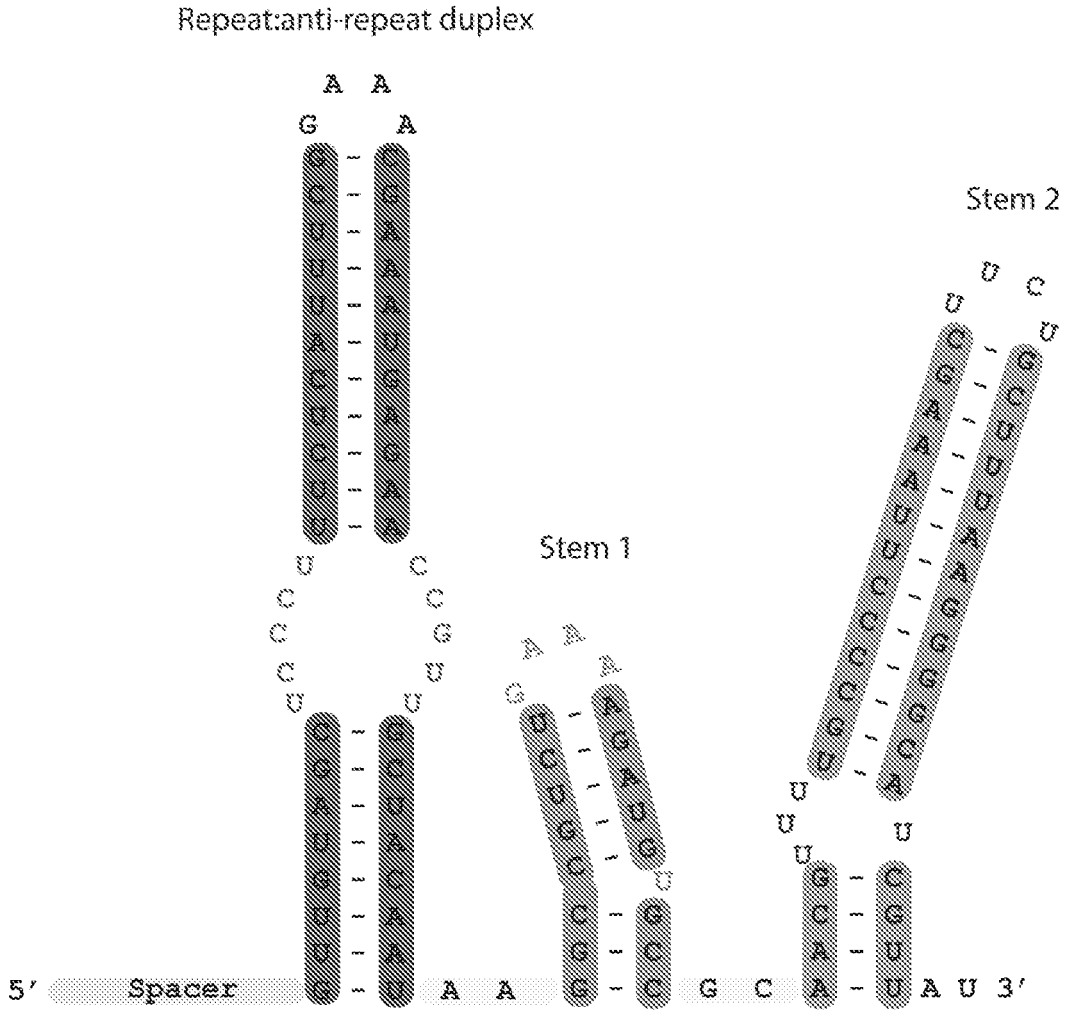


Figure 1

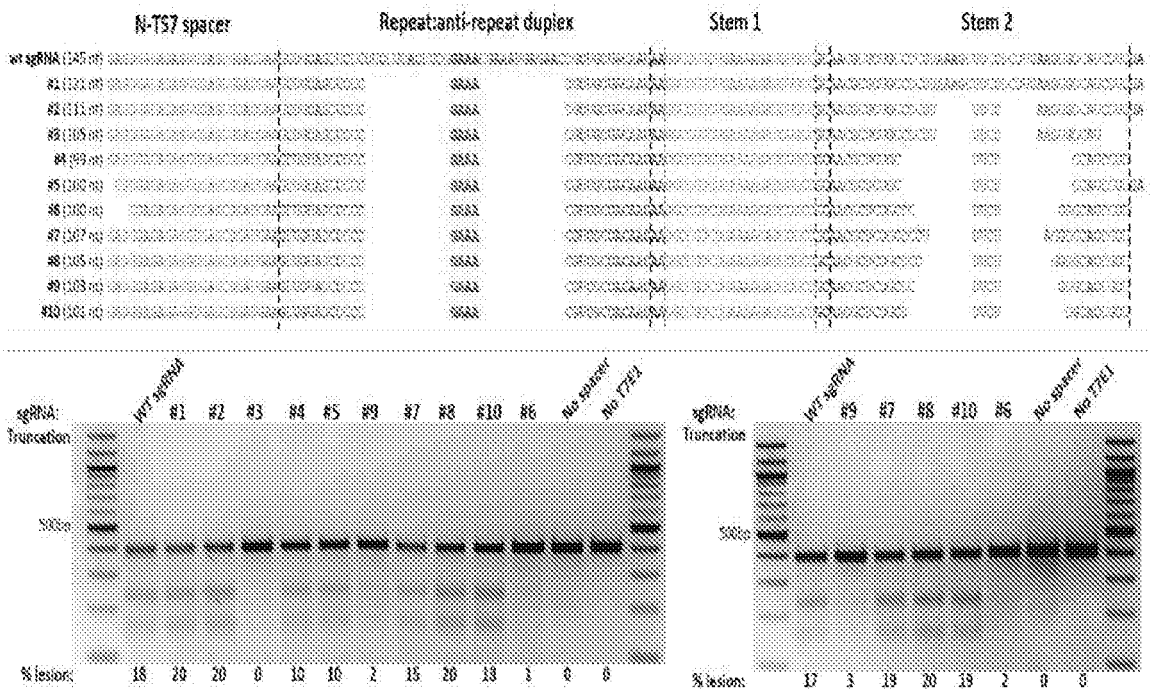

N-TS7 spacer
Repeat:anti-repeat duplex
Stem 1
Stem 2
sgRNA:
Truncation
% lesion:
WT sgRNA
#1
#2
#3
#4
#5
#9
#7
#8
#10
#6
No spacer
No T7E1
18 20 20 0 10 10 2 15 20 13 1 0 0
17 3 19 20 19 2 0 0

Figure 2

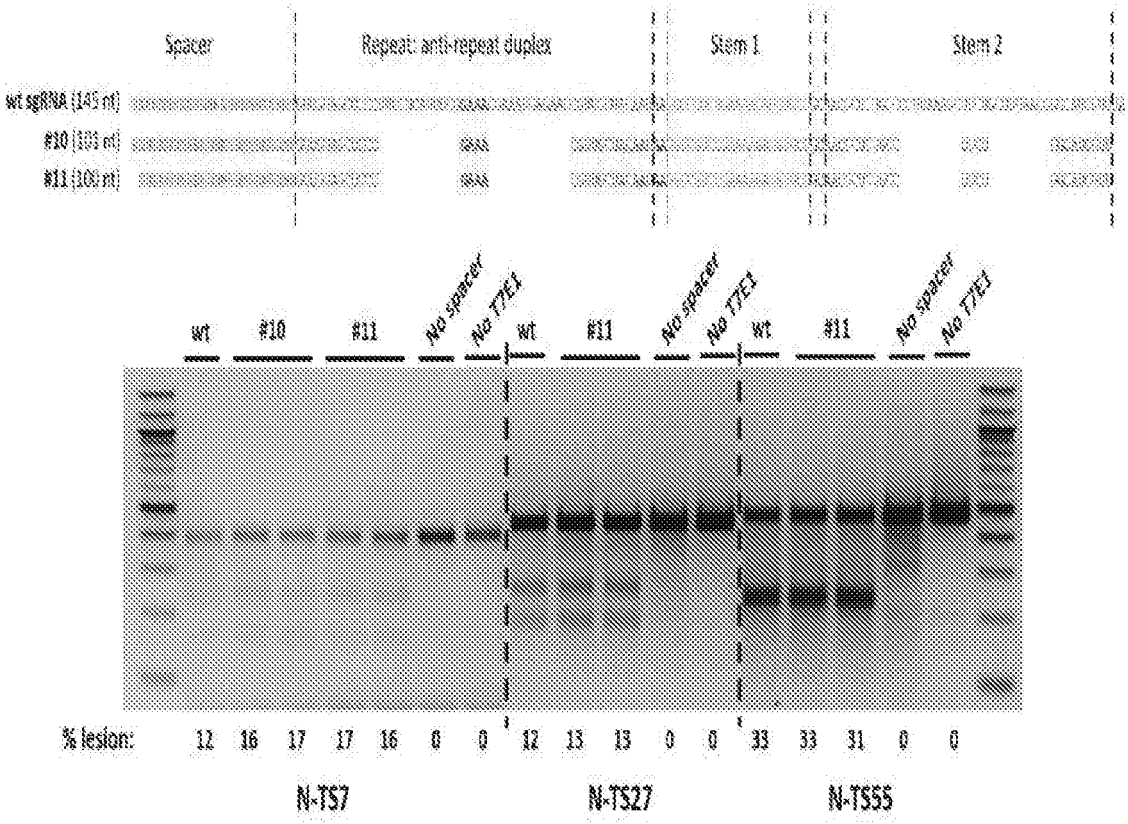

Spacer
Repeat: anti-repeat duplex
Stem 1
Stem 2
wt sgRNA (145 nt)
#10 (103 nt)
#11 (100 nt)
wt
#10
#11
No spacer
No T7E1
wt
#11
No spacer
No T7E1
wt
#11
No spacer
No T7E1
% lesion:
12 16 17 17 16 0 0 12 13 13 0 0 33 33 31 0 0
N-TS7
N-TS27
N-TS55

Figure 3

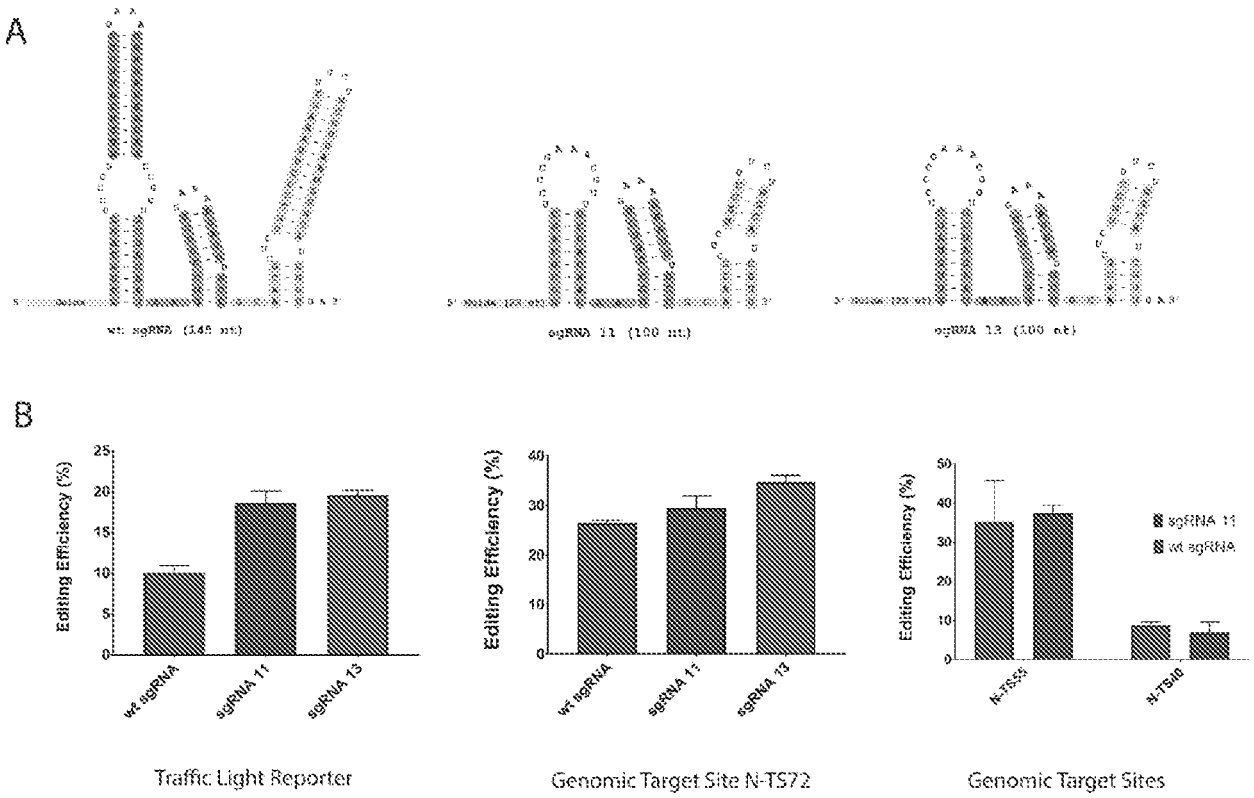
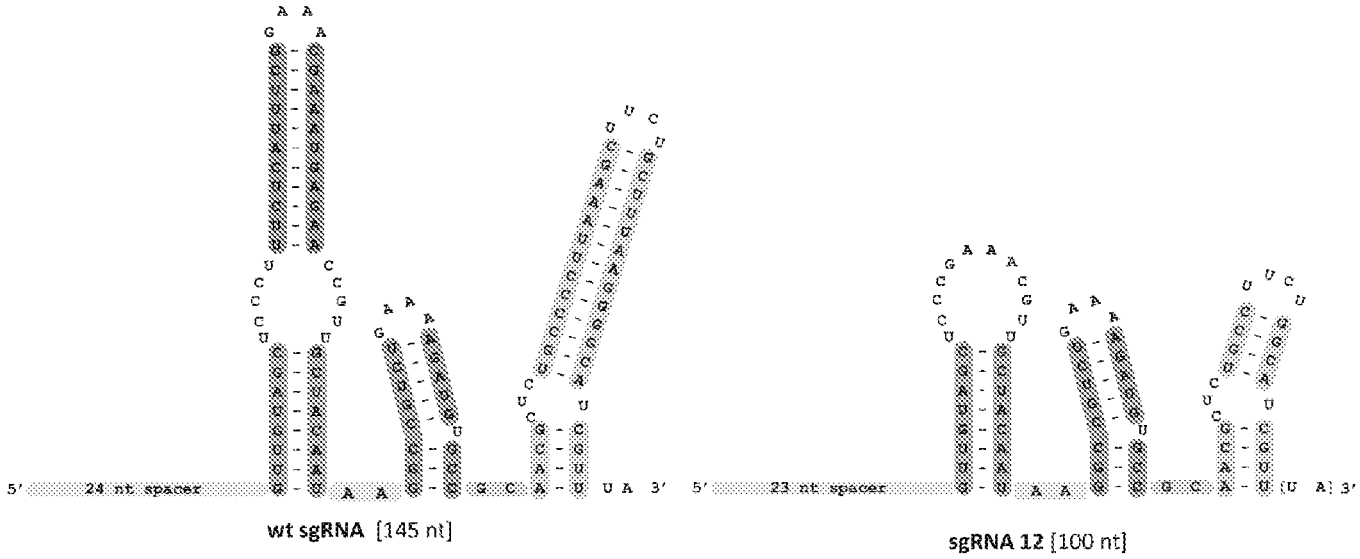

A
wt sgRNA (145 nt)
sgRNA 11 (100 nt)
sgRNA 13 (100 nt)
B
Editing Efficiency (%)
wt sgRNA
sgRNA 11
sgRNA 13
Traffic Light Reporter
Genomic Target Site N-TS72
N-TS55
N-TS48
sgRNA 11
wt sgRNA
Genomic Target Sites

Figure 4

C



D

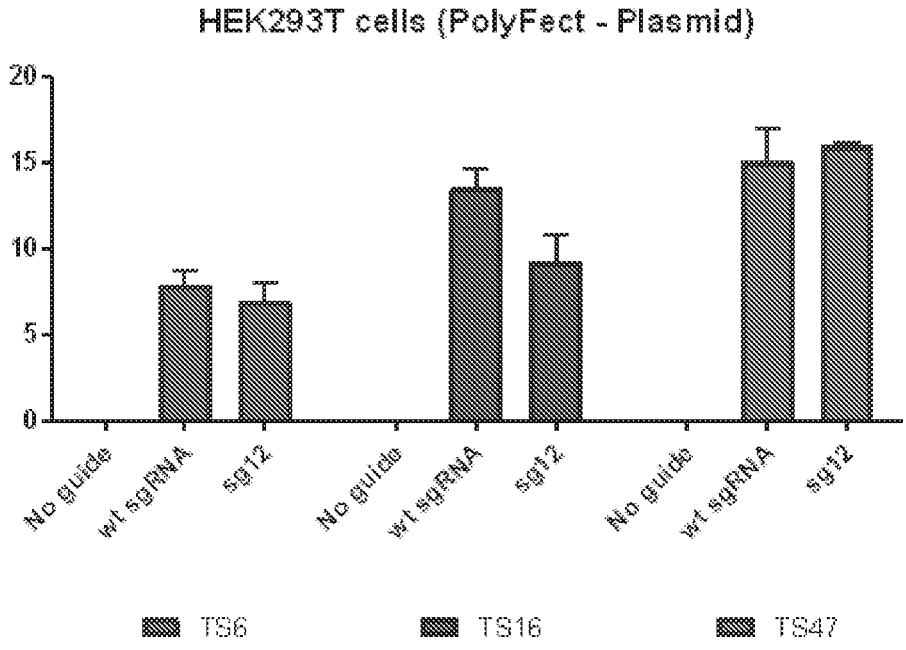


Figure 4 (cont'd)

E

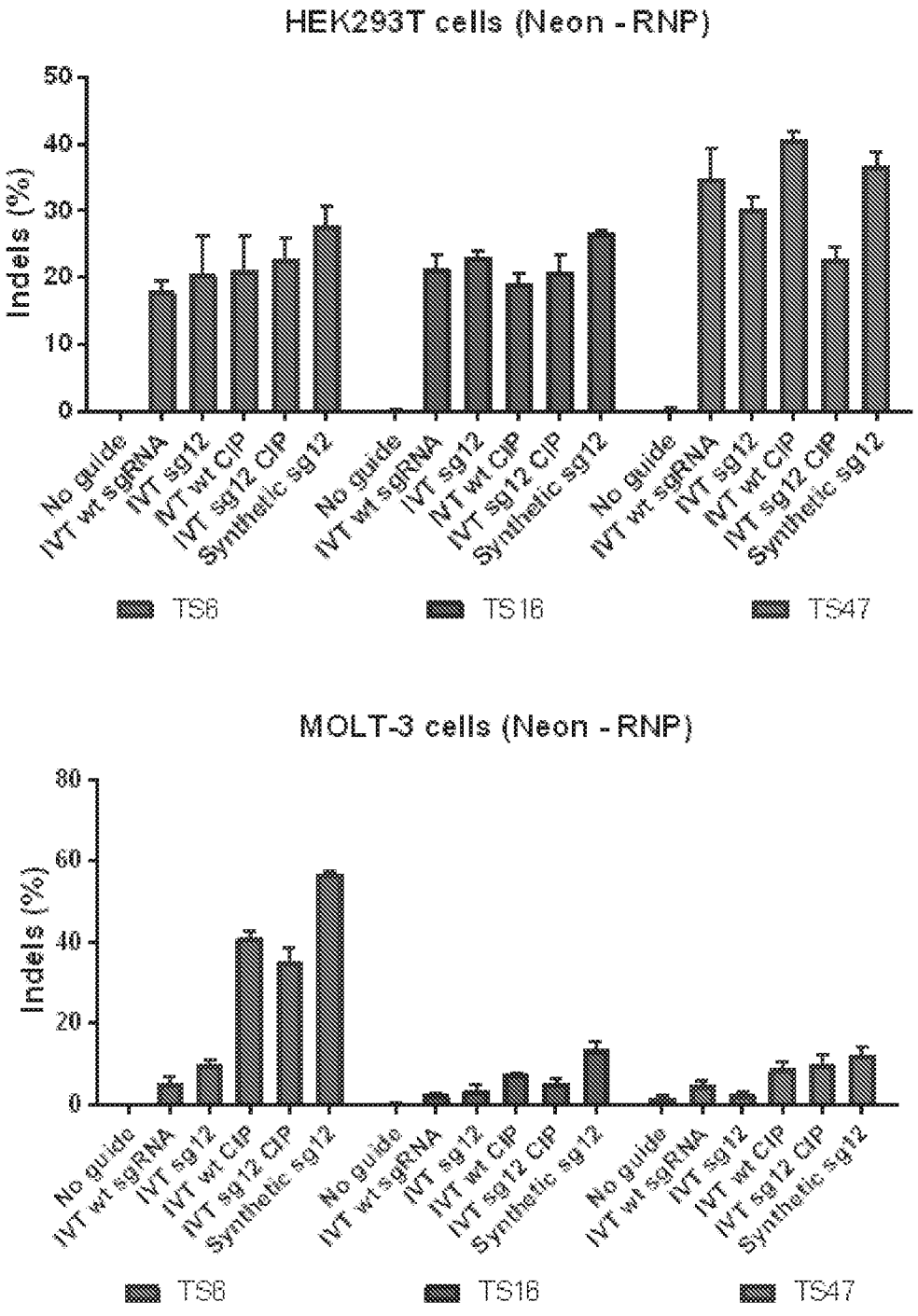


Figure 4 (cont'd)

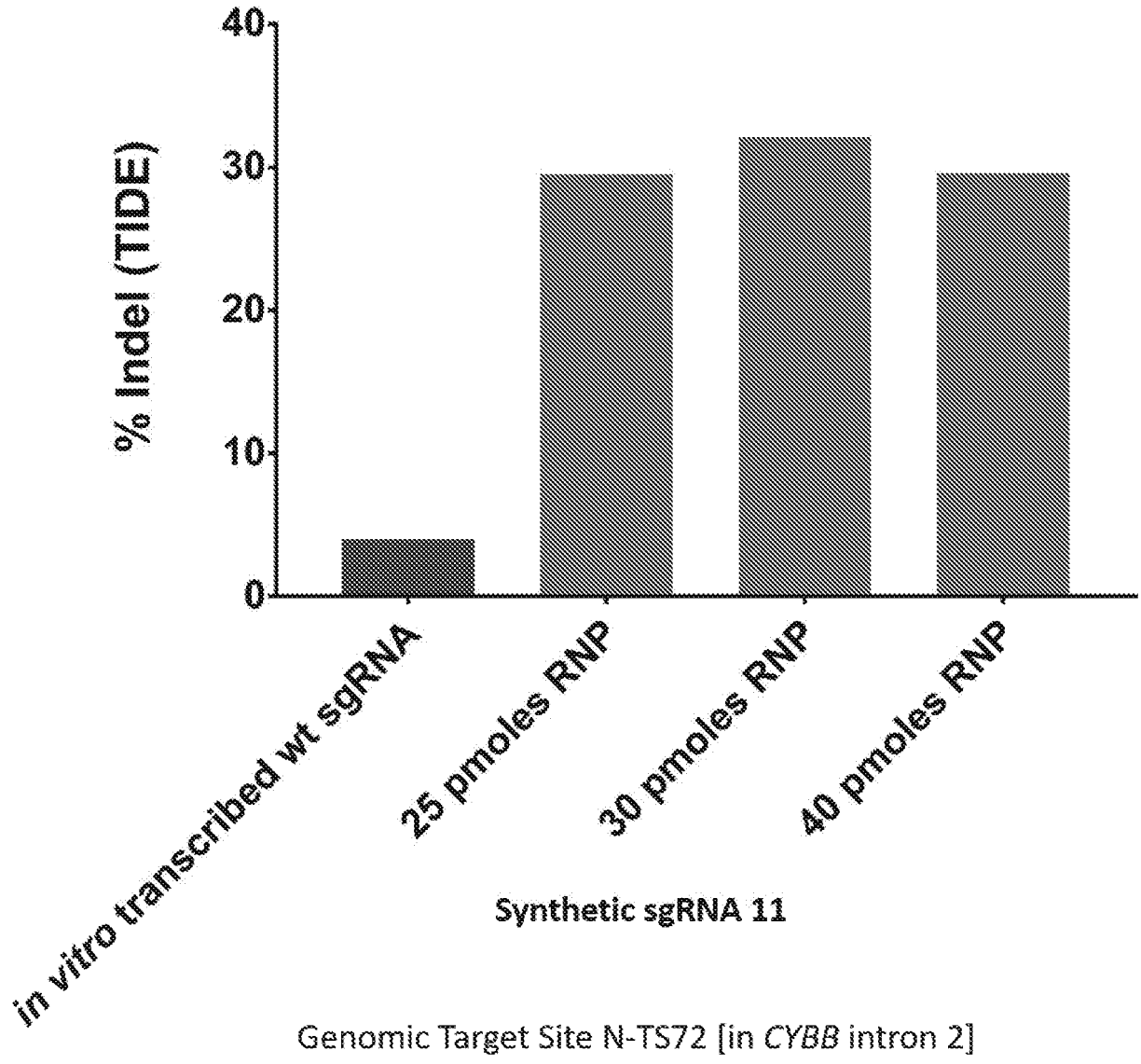
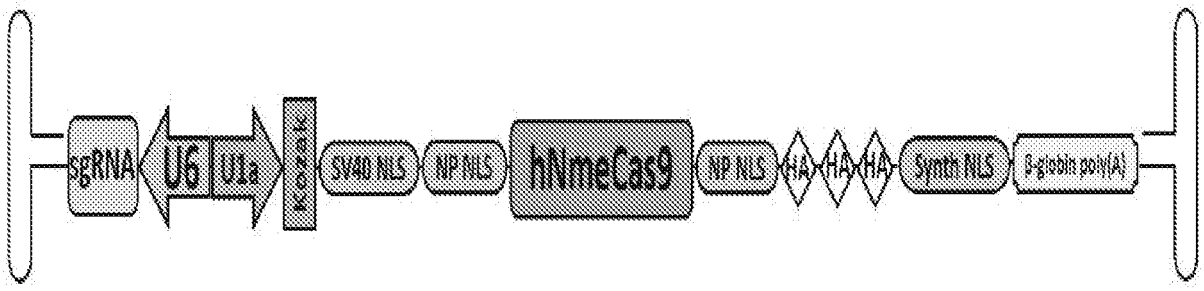
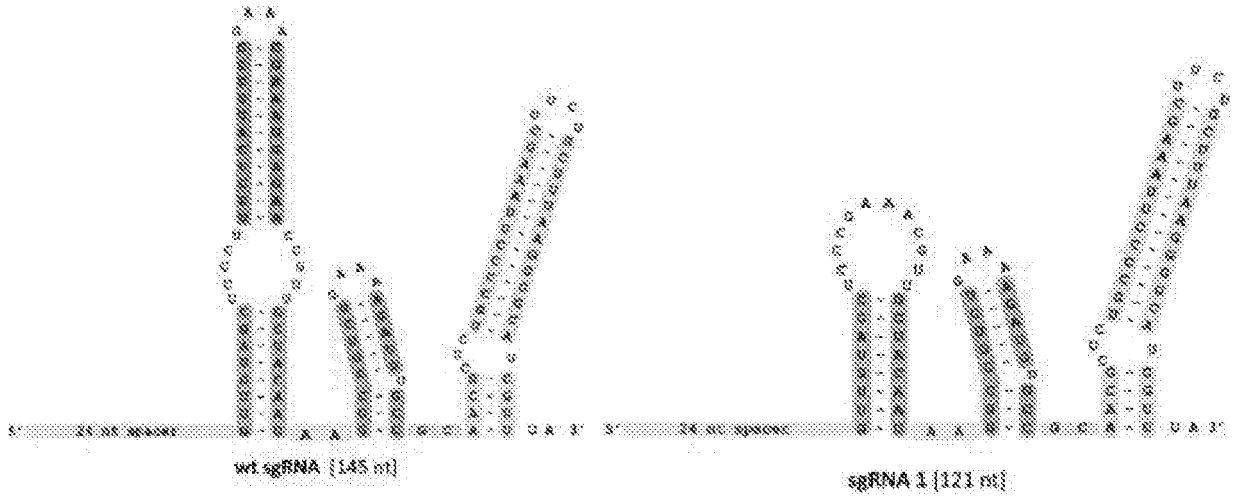

40
30
20
10
0
% Indel (TIDE)
in vitro transcribed wt sgRNA
25 pmoles RNP
30 pmoles RNP
40 pmoles RNP
Synthetic sgRNA 11
Genomic Target Site N-TS72 [in CYBB intron 2]

Figure 5

A


sgRNA
U6
U1a
spacer
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

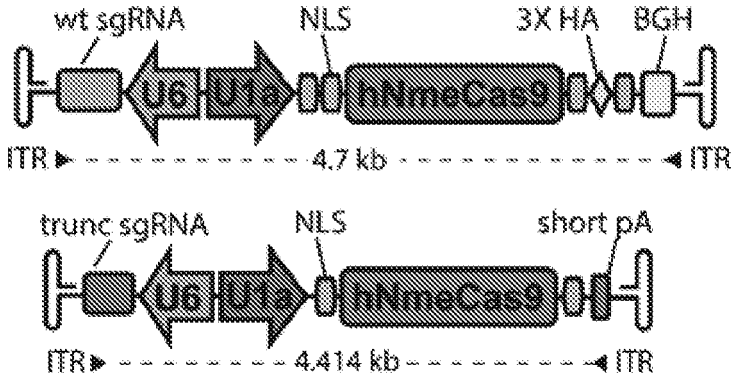

wt sgRNA
NLS
3X HA
BGH
U6
U1a
hNmeCas9
ITR
4.7 kb
ITR
trunc sgRNA
NLS
short pA
U6
U1a
hNmeCas9
ITR
4.414 kb
ITR

Figure 6

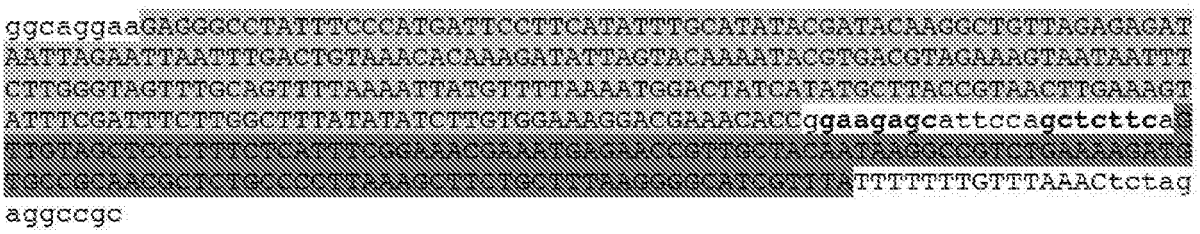
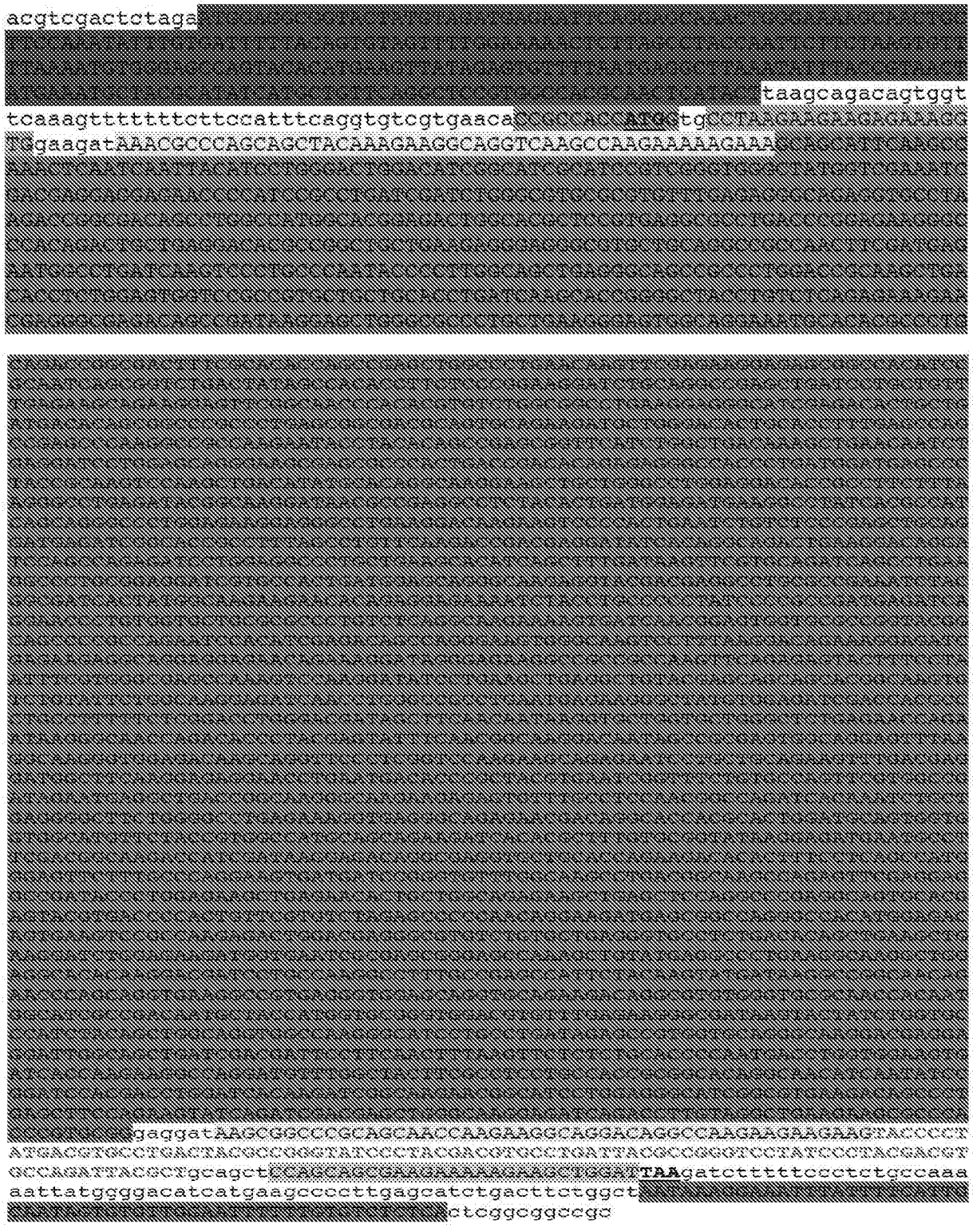

ggcaggaaGACGGCCTATTTCCCATGATTCCTTCATATTTGCATATACGATACAAGGCTGTTAGAGAGAT
AATTAGAATTAATTTGACTGTAAACACAAAGATATTAGTACAAAATACGTGACGTAGAAAGTAATAATTT
CTTGGGTAGTTTGCAGTTTTAAAATTATGTTTTAAAATGGACTATCATATGCTTACCGTAACTTGAAAGT
ATTTCGATTTCTTGGCTTTATATATCTTGTGGAAAGGACGAAACACCGgaagagcattccagctcttca
TTTTTTTGTTTAAACtctag
aggccgc

Figure 7

acgtcgactctaga[redacted]taagcagacagtggt
tcaaagtttttttcttccatttcaggtgtcgtgaaca[redacted]tgCCTAAGAAGAAGAGAAAGG
TGgaagatAAACGCCCAGCAGCTACAAAGAAGGCAGGTCAAGCCAAGAAAAAGAAA[redacted]



[redacted]gaggatAAGCGGCCCGCAGCAACCAAGAAGGCAGGACAGGCCAAGAAGAAGAAGTACCCCT
ATGACGTGCCTGACTACGCCGGGTATCCCTACGACGTGCCTGATTACGCCGGGTCCTATCCCTACGACGT
GCCAGATTACGCTgcagct[redacted]TAAgatctttttccctctgccaaa
aattatggggacatcatgaagccccttgagcatctgacttctggct[redacted]ctcggcggccgc

Figure 8

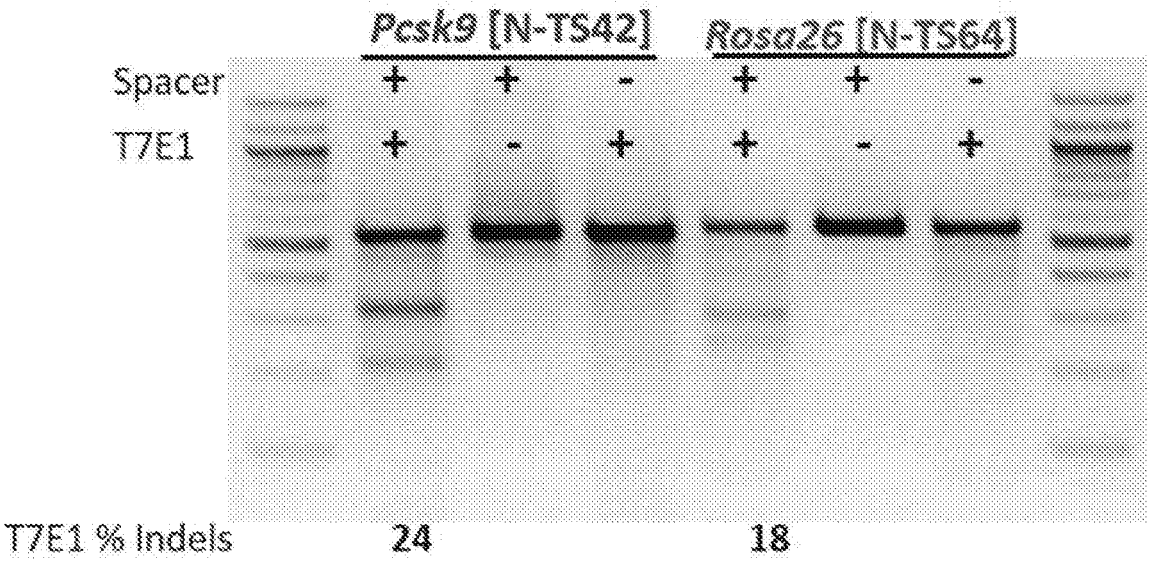


Figure 9

Pcsk9

TGGCGTGATCTCCCGGCCCCCAGGCGTCCAGTACCCACACCCCCAGAAGGCTTCCACCTTCACGTGGACGC
GCAGGCTGCCGGTGGGCTCCCGTTCTCTCTCTCTTTCTGAGGCTAGAGGACTGAGCCAGTCCTTGGCTCC
CCAGAGACATCACGGCCCGCAGCCCCGGAGCCAAGTGCCCCGAGTCCCAGGCGTCCATGTCCTTCCCGAG
GCCGCGCGCACCTCTCCTCGCCCCGATGGGCACCCACTGCTCTGCGTGGCTGCGGTGGCCGCTGTTGCCG
CTGTTGCCGCCGCTGCTGCTGCTGTTGCTGCTACTGTGCCCCACCGGCGCTGGTGCCCAGGACGAGGATG
GAGATTATGAAGAGCTGATGCTCGCCCTCCCGTCCCAGGAGGATGGCCTGGCTGATGAGGCCGCACATGT
GGCCACCGCCACCTTCCGCCGTTGCTCCAAGGTATGGGTGCCAGGCAACGGCGTTGCTTTGGGGTTGGGG
TGATGCTCTTCGGGGGTCTTCTCTGCTCATCTAGCCGTCTGGTGGTCTCTAAGTGCAGCCCTGAGGTGCG
GGAGGCGAGGGCAAGACTTAGTGCTCAGCTGCACCTTGTGGCACAGAGTGATGGGGGAGGCCACGTGCTA
AAGGCACTGCGGGGCTTGGTTCCAAAAGTGTGAGGCGGGGAGCGGGCTACCAGTGTGGTCATGCAGAAAA
CGTGTCCTCCGAAGTAAAGTGGCATCGGGAGGCTGAGAACTCTAGTGGCACATCTTTCTCAACTGGTCAT
CCAGCAGTCATCCTGGGTGCCTGTTGGGGTTCTGTAGGCCTCGATTTAGCGGAAGGGTGTCAGGG

Rosa26

GGAAAGGGAAAATGCCAATGCTCTGTCTAGGGGTTGGATAAGCCAGTATAATAAATGAAAATGGGGCTAA
AATGAGTGTTCTAAAATACCTTTTGATAAGGCTGCAGAAGGAGCGGGAGAAATGGATATGAAGTACTGGG
CTCTTTAAAAATGATTAAAATTCTGCTTACATAGTCTAACTCGCGACACTGTAATTTCATACTGTAGTAA
GGATCTCAAGCAGGAGAGTATAAAACTCGGGTGAGCATGTCTTTAATCTACCTCGATGGAAAATACTCCG
AGGCGGATCACAAGCAATAATAACCTTTAGTTTTGCTGCATAAAACCCCAGATGACTACCTATCCTCCCA
TTTTCCTTATTTGCCCCTATTAAAAAACTTCCCGACAAAACCGAAAATCTGTGGGAAGTCTTGTCCCTCC
AATTTTACACCTGTTCAATTCCCCTGCAGGACAACGCCCACACACCAGGTTAGCCTTTAAGCCTGCCCAG
AAGACTCCCGCCCATCTTCTAGAAAGACTGGAGTTGCAGATCACGAGGGAAGAGGGGGAAGGGATTCTCC
CAGGCCCAGGGCGGTCCTCAGAAGCCAGGAGGCAGCAGAGAACTCCCAGAAAGGTATTGCAACACTCCCC
TCCCCCCTCCGGAGAAGGGTGCGGCCTTCTCCCCGCCTACTCCACTGCAGCTCCCTTACTGATAACAACT
CAGAGCGACTTTGGGAGAGCAAGTGCTTCCTGCCTCCAAAACAGCCCAACTGAGCCCTCGCTCCTTCCCT
CCACTCCCCGGAGTGCGCGATGGAGGTCTGGCTCAGCACGCCCCTCTTGAGGCAACTCAAGTCGGAAACG
TGCTTCCACCCGCCCCGCAGCCG

Figure 10

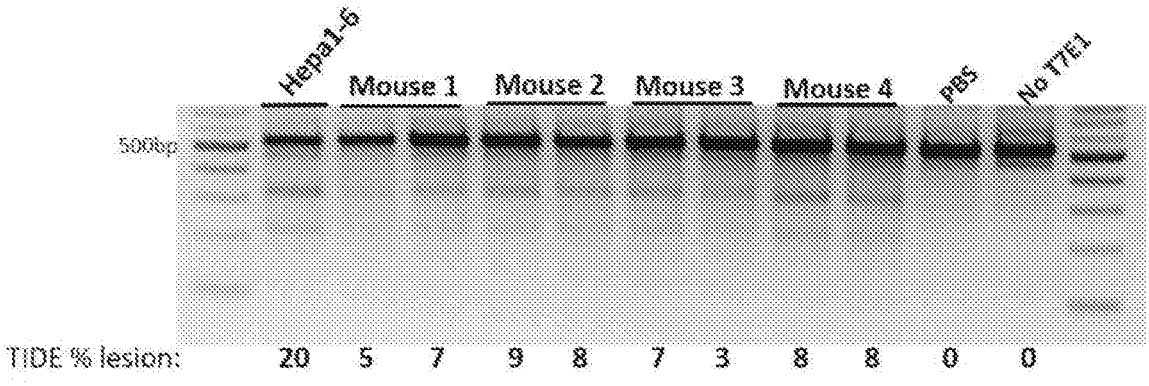

Hepa1-6
Mouse 1
Mouse 2
Mouse 3
Mouse 4
PBS
No T7E1
500bp
TIDE % lesion:
20 5 7 9 8 7 3 8 8 0 0

Figure 11

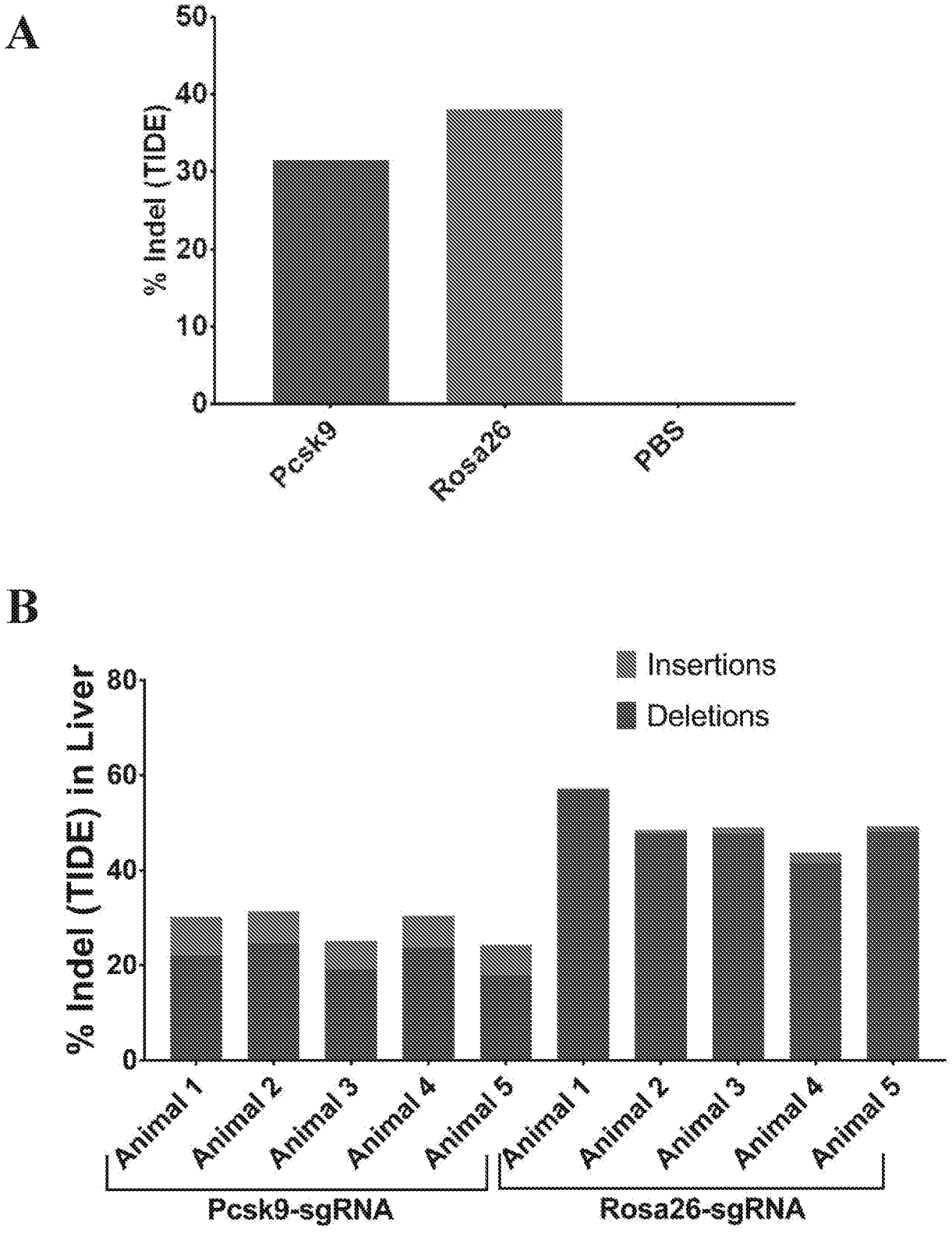

A
% Indel (TIDE)
50
40
30
20
10
0
Pcsk9
Rosa26
PBS
B
% Indel (TIDE) in Liver
80
60
40
20
0
Insertions
Deletions
Animal 1
Animal 2
Animal 3
Animal 4
Animal 5
Animal 1
Animal 2
Animal 3
Animal 4
Animal 5
Pcsk9-sgRNA
Rosa26-sgRNA

Figure 12

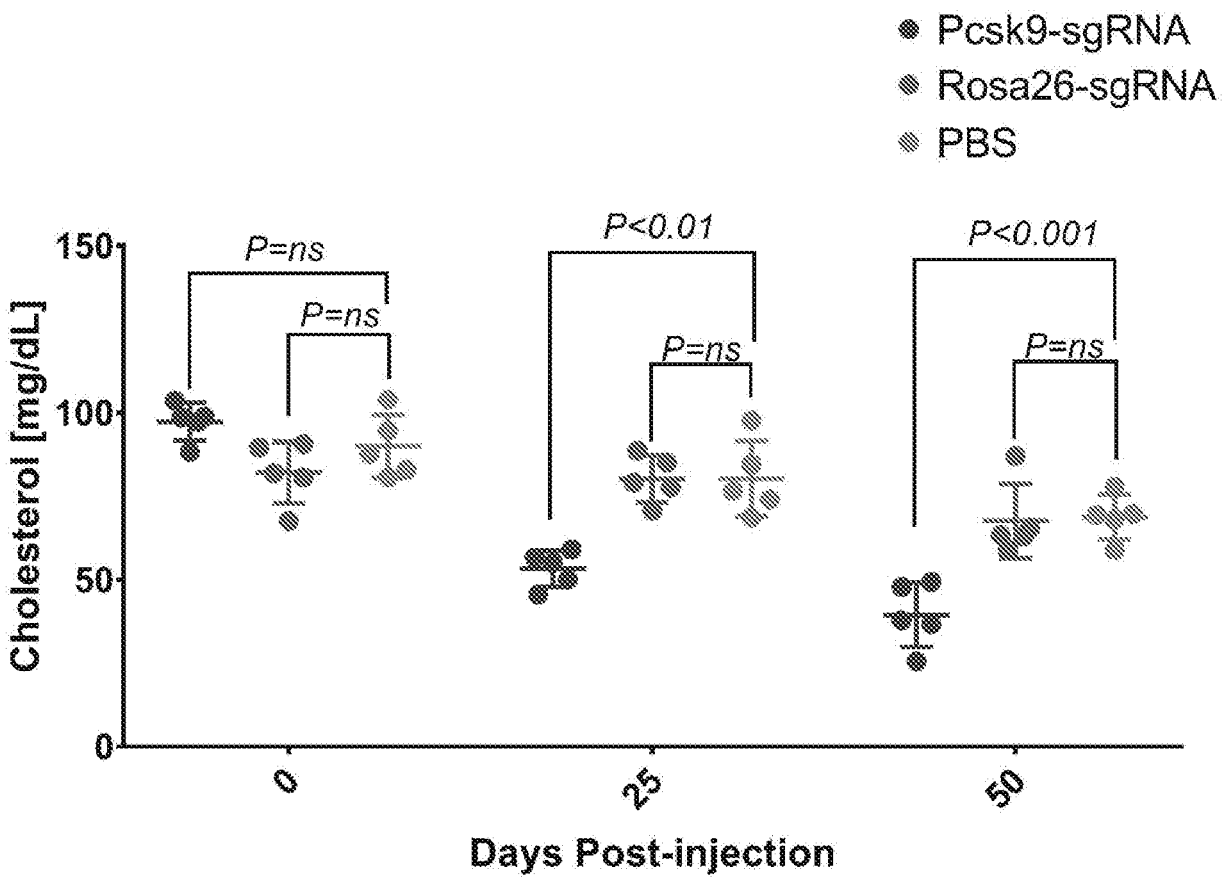
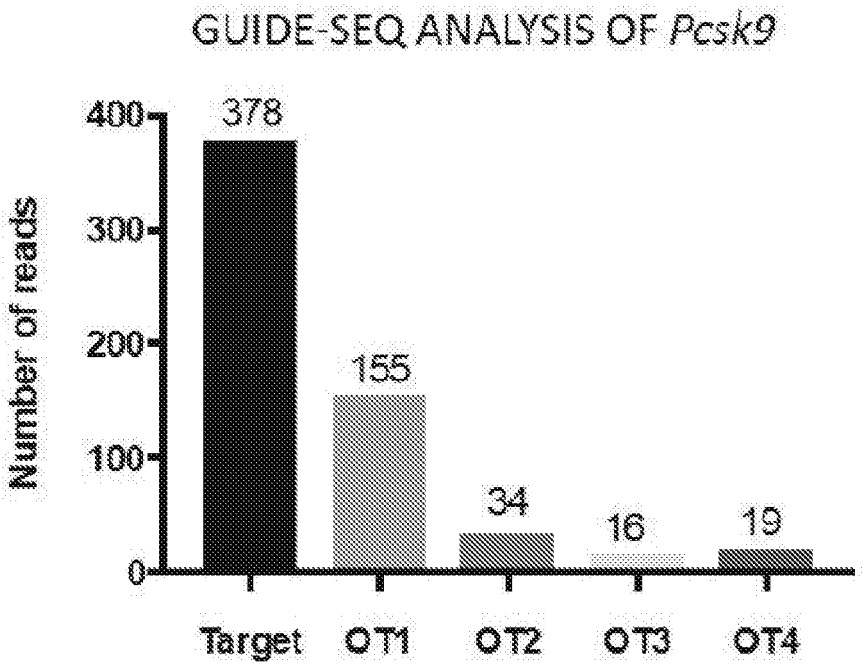

Pcsk9-sgRNA
Rosa26-sgRNA
PBS
Cholesterol [mg/dL]
150
100
50
0
P=ns
P=ns
P<0.01
P=ns
P<0.001
P=ns
0
25
50
Days Post-injection

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

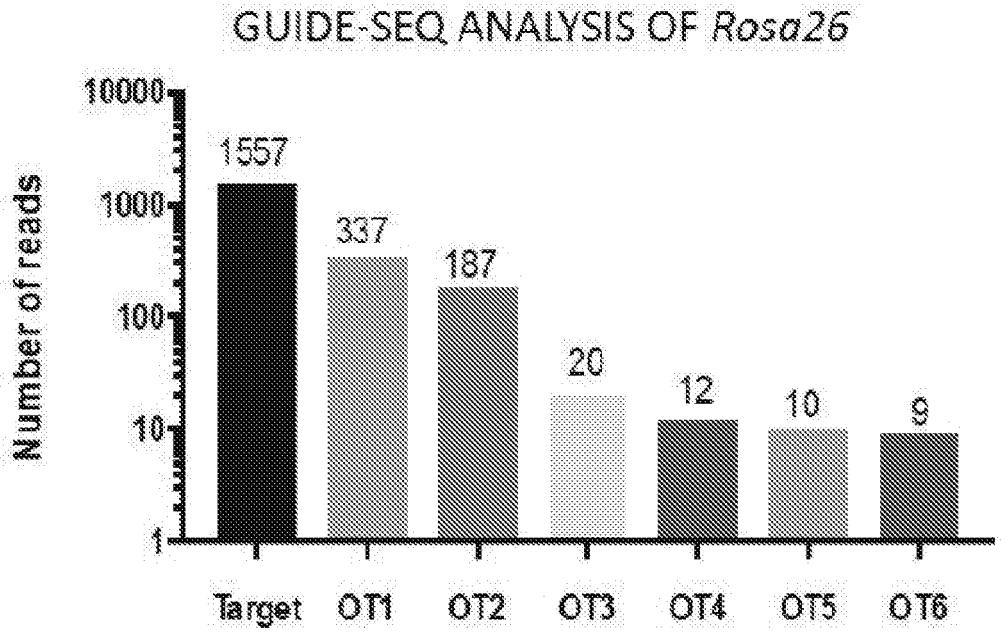

GUIDE-SEQ ANALYSIS OF Rosa26
Number of reads
10000
1000
100
10
1
1557
337
187
20
12
10
9
Target
OT1
OT2
OT3
OT4
OT5
OT6

Figure 14

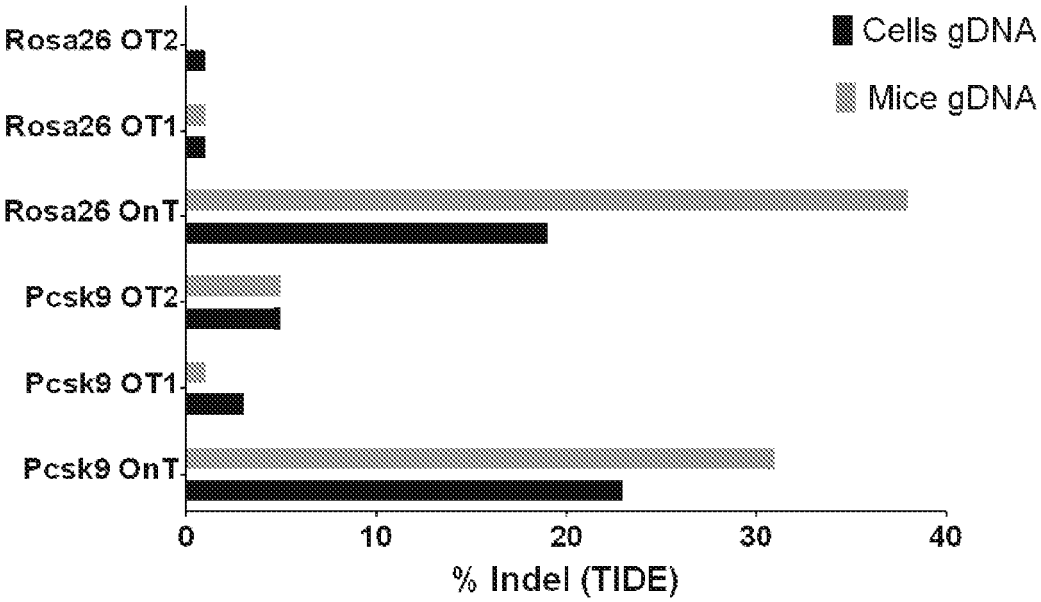

Rosa26 OT2
Rosa26 OT1
Rosa26 OnT
Pcsk9 OT2
Pcsk9 OT1
Pcsk9 OnT
Cells gDNA
Mice gDNA
0
10
20
30
40
% Indel (TIDE)

Figure 15

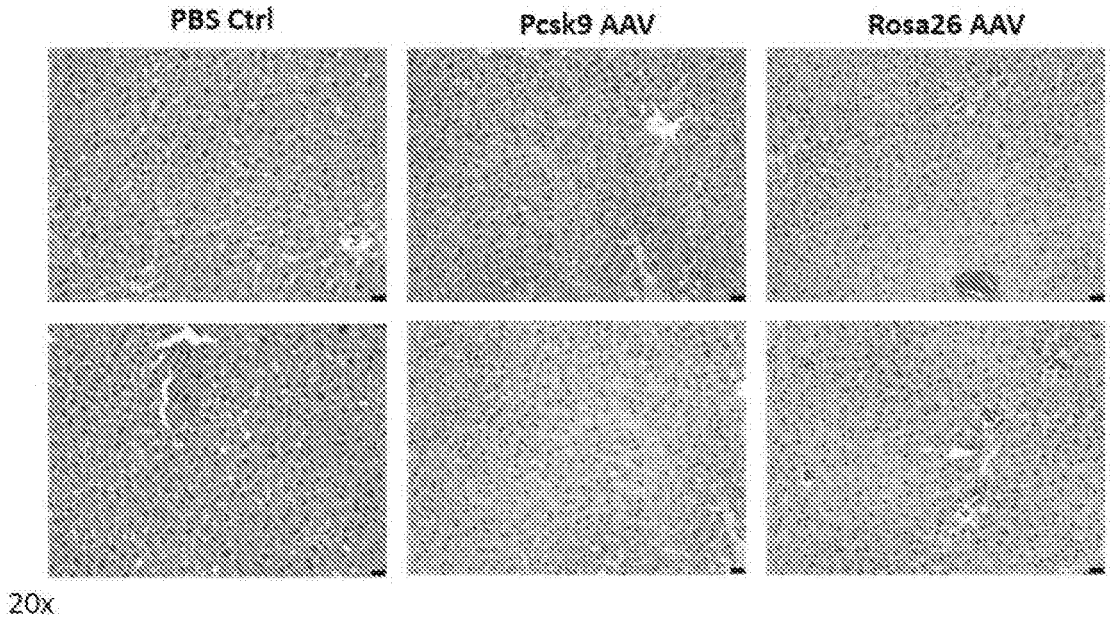


Figure 16

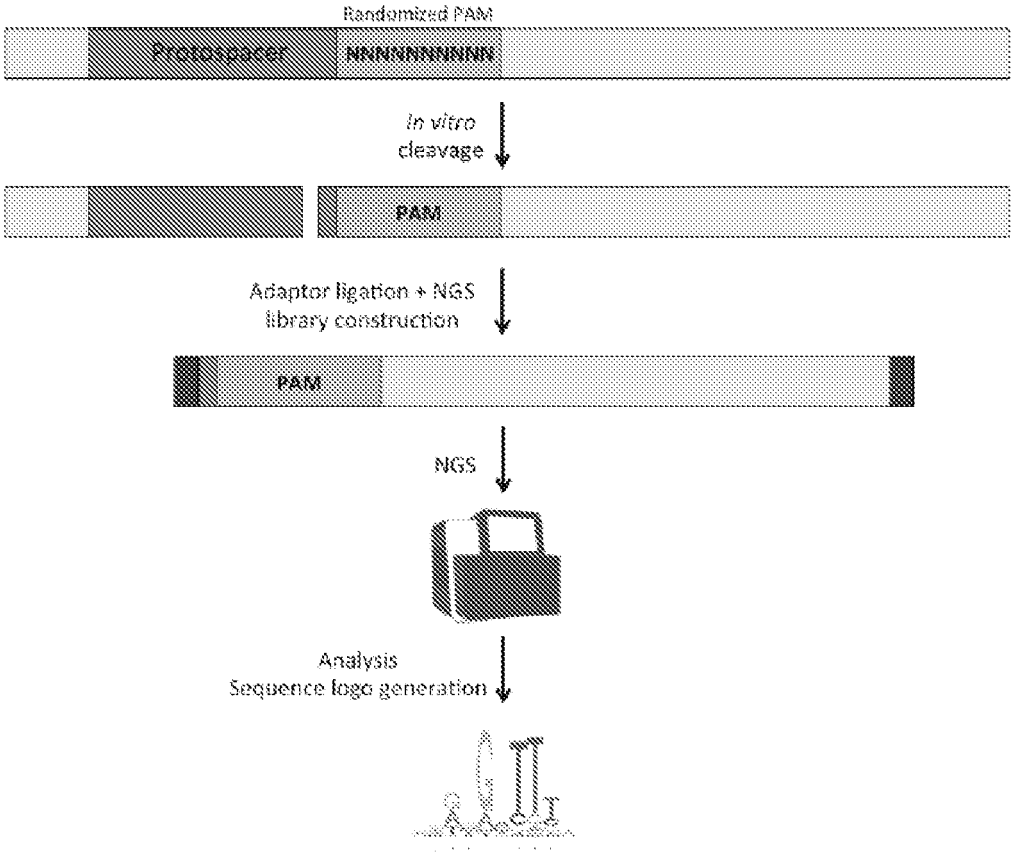

Randomized PAM
Protospacer
NNNNNNNNNN
In vitro
cleavage
PAM
Adaptor ligation + NGS
library construction
PAM
NGS
Analysis
Sequence logo generation

Figure 17

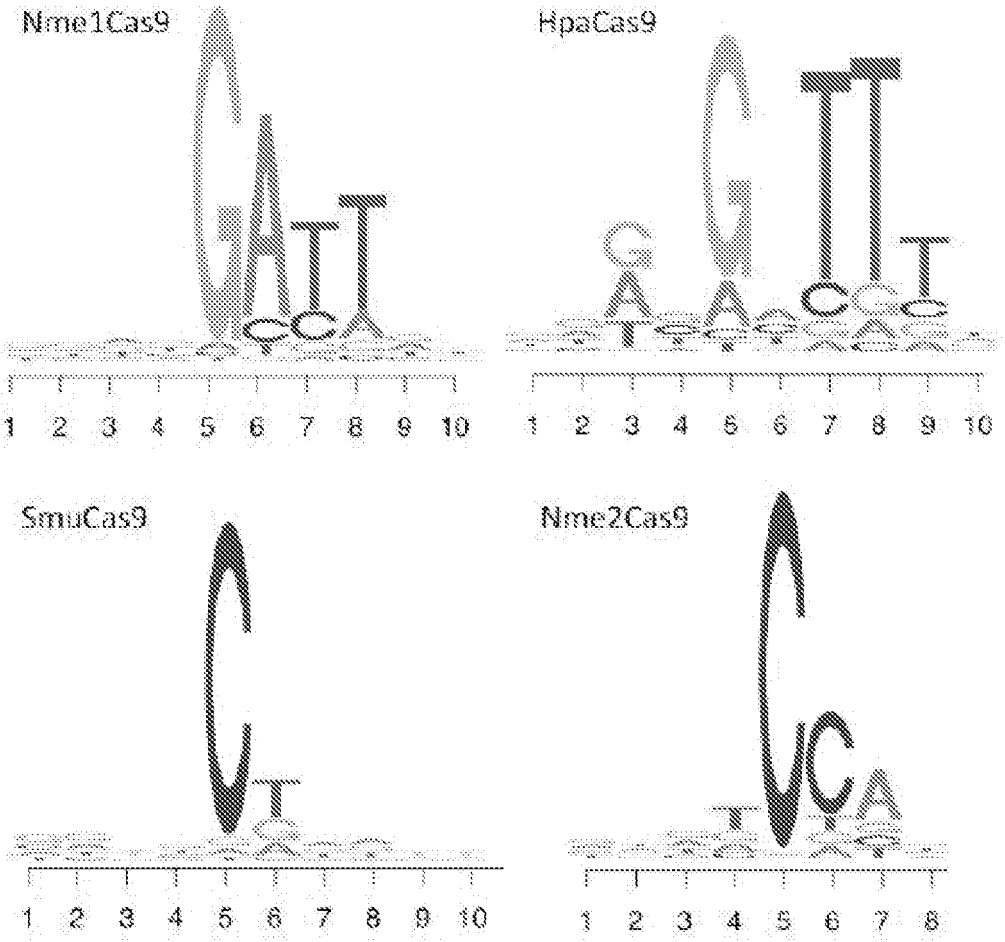

Nme1Cas9
1 2 3 4 5 6 7 8 9 10
HpaCas9
1 2 3 4 5 6 7 8 9 10
SmuCas9
1 2 3 4 5 6 7 8 9 10
Nme2Cas9
1 2 3 4 5 6 7 8

Figure 18

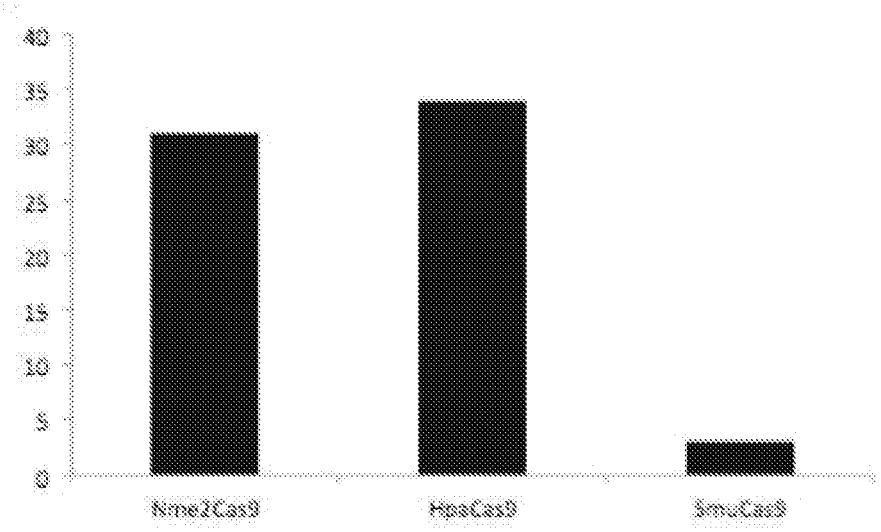


Figure 19

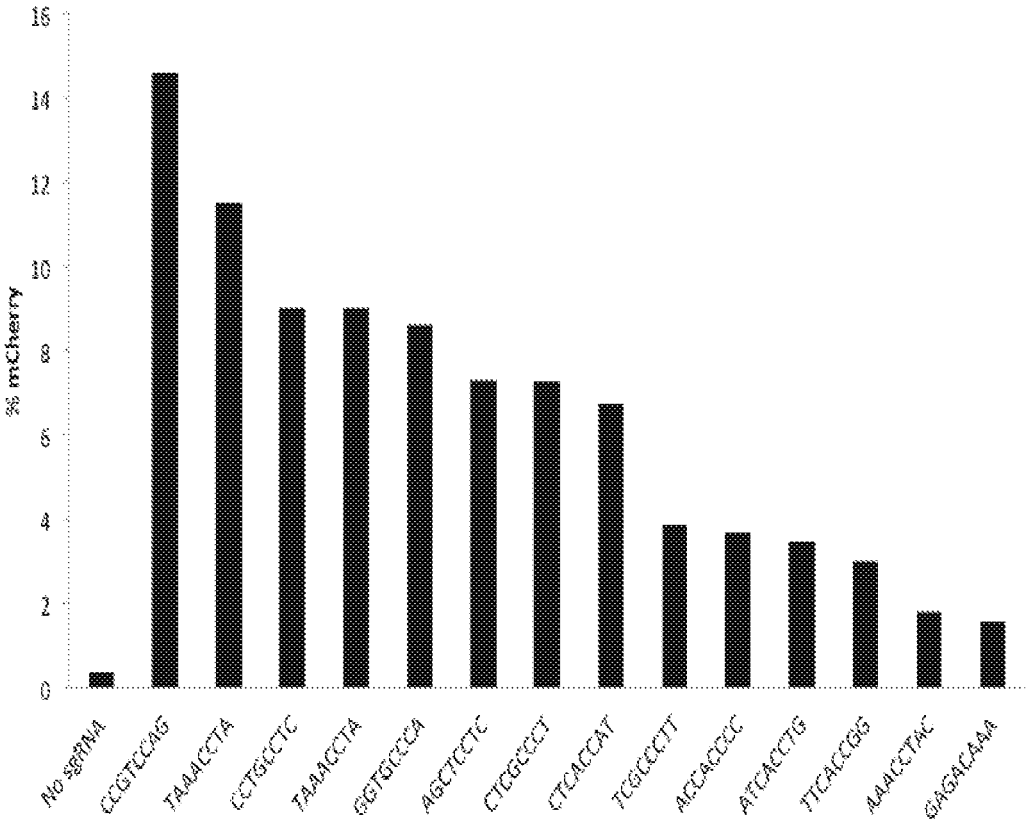

% mCherry
16
14
12
10
8
6
4
2
0
No sgRNA
CCGTCCAG
TAAACCTA
CCTGCCTC
TAAACCTA
GGTGCCCA
AGCTCCTC
CTCGCCCT
CTCACCAT
TCGCCCTT
ACCACCCC
ATCACCTG
TTCACCGG
AAACCTAC
GAGACAAA

Figure 20

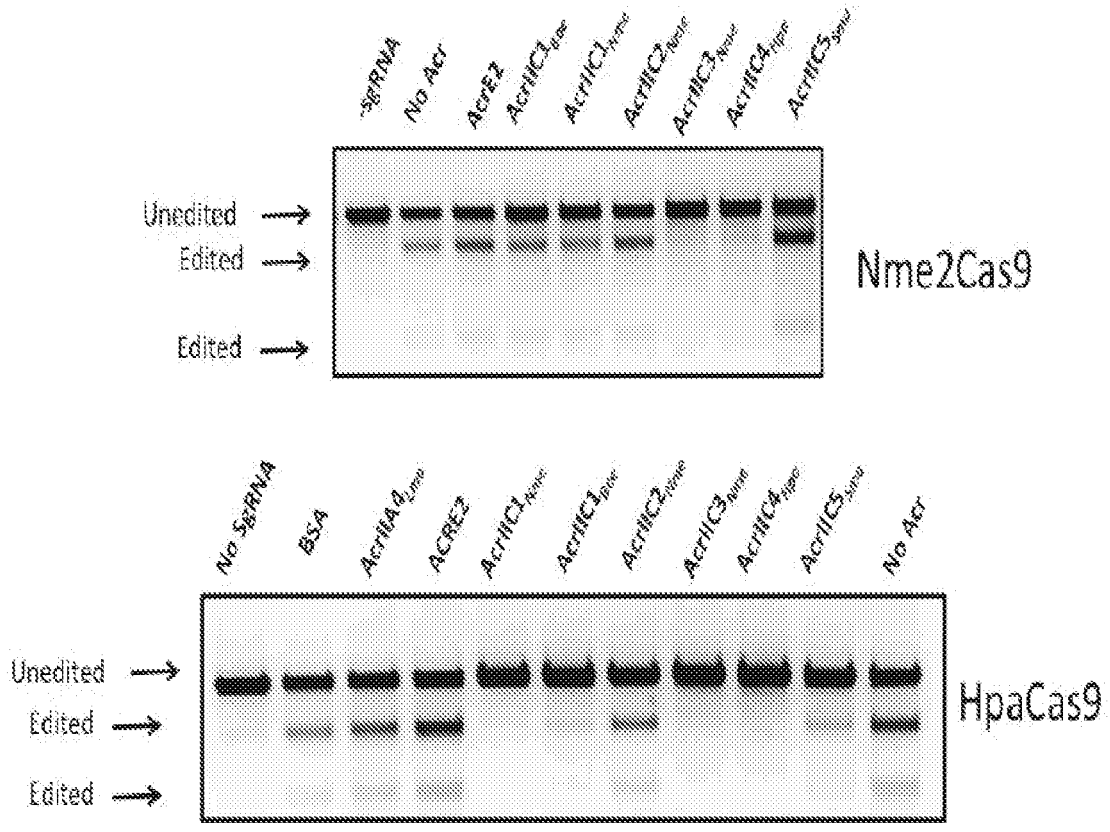

-sgRNA
No Acr
AcrIIC1
AcrIIC3
AcrIIC2
AcrIIC3
AcrIIC4
AcrIIC5
Unedited
Edited
Edited
Nme2Cas9
No SgRNA
BSA
AcrIIA4
ACRE2
AcrIIC1
AcrIIC3
AcrIIC2
AcrIIC3
AcrIIC4
AcrIIC5
No Acr
Unedited
Edited
Edited
HpaCas9

Figure 21

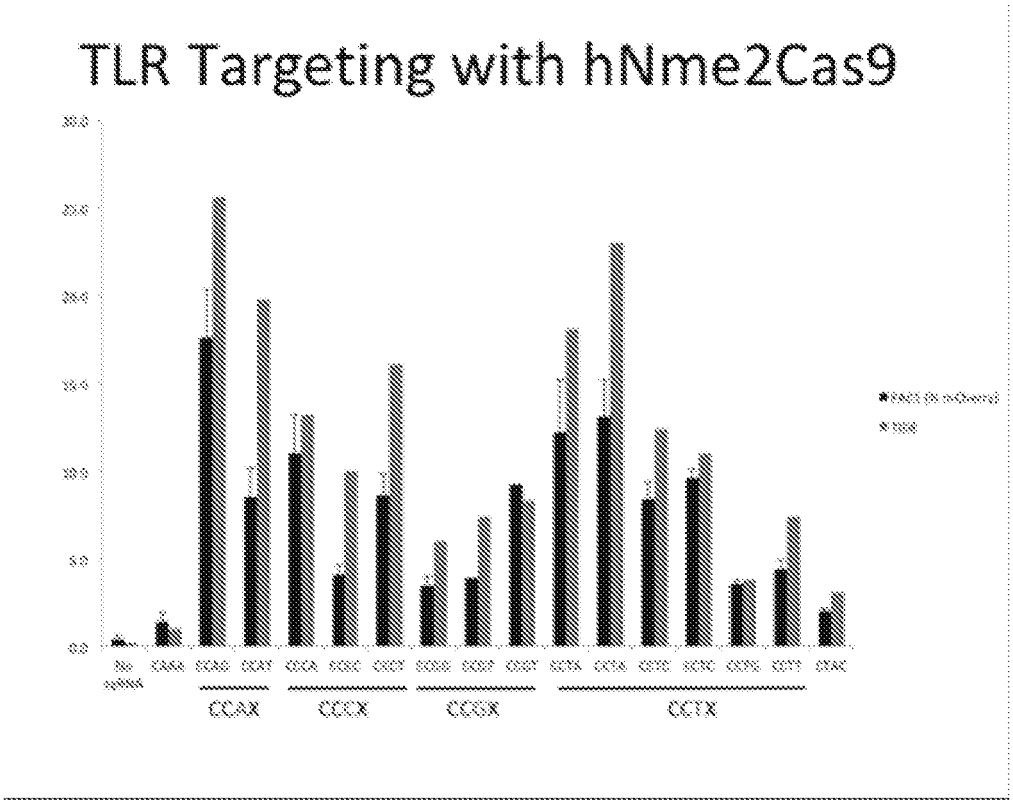


Figure 22

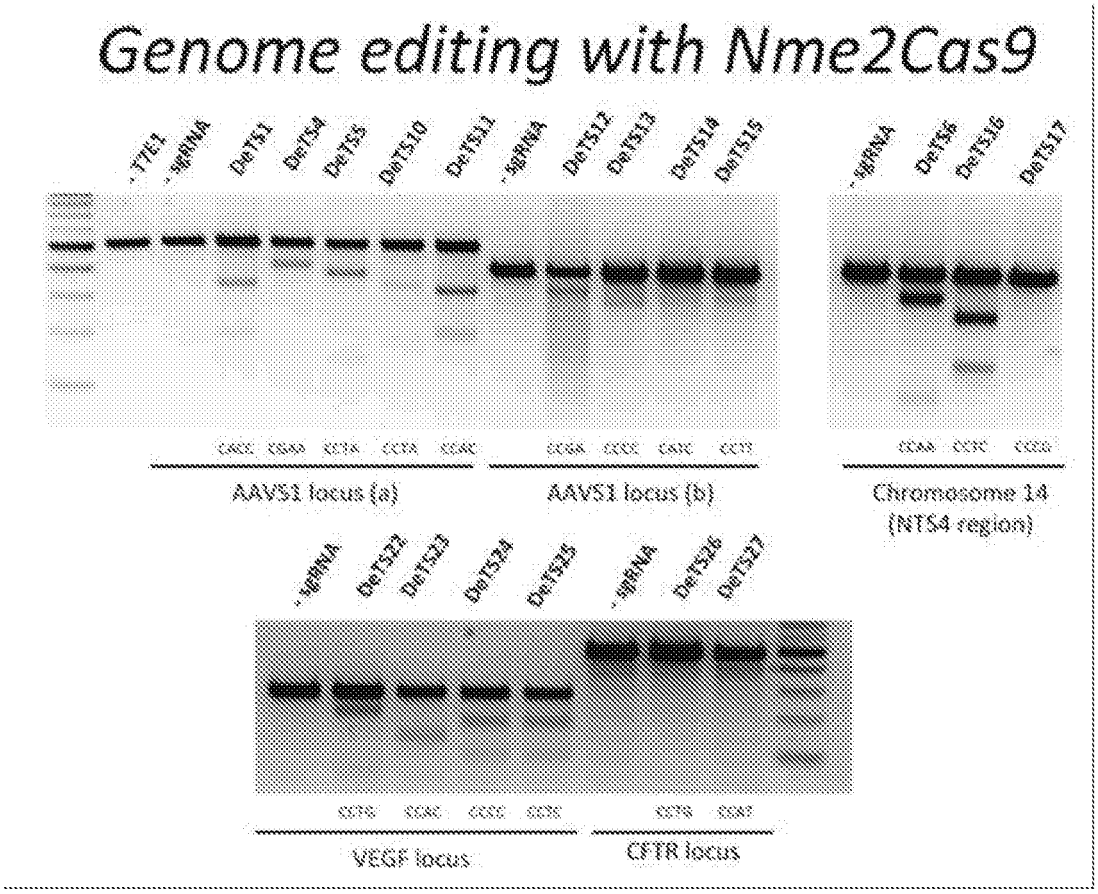

Genome editing with Nme2Cas9
- T7E1
- sgRNA
DeTS1
DeTS4
DeTS5
DeTS10
DeTS11
- sgRNA
DeTS12
DeTS13
DeTS14
DeTS15
- sgRNA
DeTS16
DeTS17
AAVS1 locus (a)
AAVS1 locus (b)
Chromosome 14
(NTS4 region)
- sgRNA
DeTS22
DeTS23
DeTS24
DeTS25
- sgRNA
DeTS26
DeTS27
VEGF locus
CFTR locus

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
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Figure 24

MAAFKPNPINYILGLDIGIASVGWAMVEIDEEENPIRLIDLGVRVFERAEVPKTGDSLAM
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NAYTIADNGDMVRVDVFCKVDKKGKNQYFIVPIYAWQVAENILPDIDCKGYRIDDSYTF
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Figure 25

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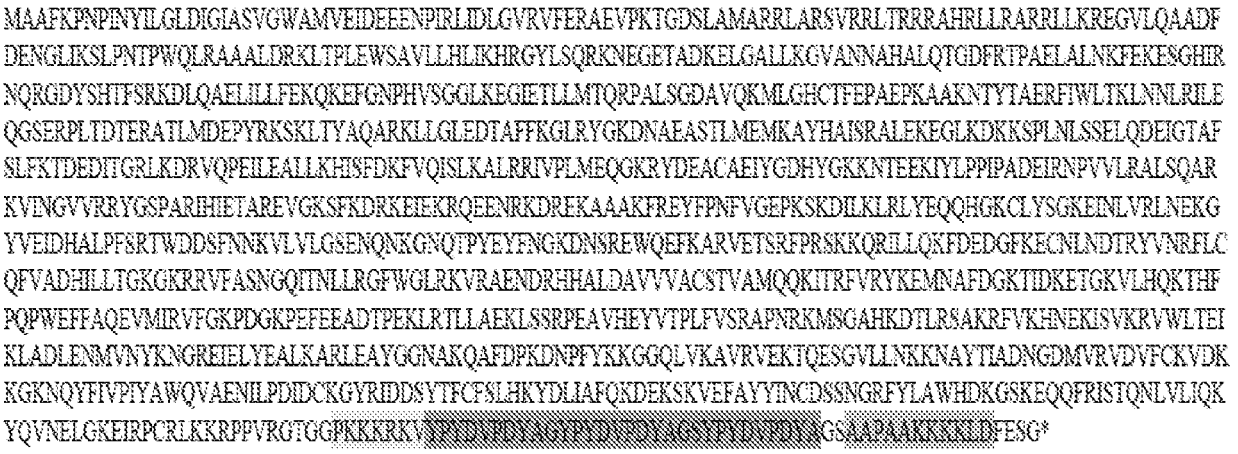
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NQRGDYSHTFSRKDLQAELILLFEKQKEFGNPHVSGGLKEGIETLLMTQRPALSGDAVQKMLGHCTFEPAEPKAAKNTYTAERFIWLTKLNNLRILE
QGSERPLTDTERATLMDEPYRKSKLTYAQARKLLGLEDTAFFKGLRYGKDNAEASTLMEMKAYHAISRALEKEGLKDKKSPLNLSSELQDEIGTAF
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QFVADHILLTGKGKRRVFASNGQITNLLRGFWGLRKVRAENDRHHALDAVVVACSTVAMQQKITRFVRYKEMNAFDGKTIDKETGKVLHQKTHF
PQPWEFFAQEVMIRVFGKPDGKPEFEEADTPEKLRTLLAEKLSSRPEAVHEYVTPLFVSRAPNRKMSGAHKDTLRSAKRFVKHNEKISVKRVWLTEI
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YQVNELGKEIRPCRLKKRPPVRGTGGPKKKRKV[redacted]GSAAPAKKSKLDFESG*

Figure 27

MENKNLNYILGLDLGIASVGWAVVEIDEKENPLRLIDVGVRTFERAEVPKTGESLALSRR
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VEEGHIRNQQGAYTHTFSRLDLLAEMELLFSRQQHFGNPFASEKLLENLTALLMWQKPA
LSGEAILKMLGKCTFEDEYKAAKNTYSAERFVWITKLNNLRIQENGLERALNDNERLAL
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EGNNLKAEWAELKANPTLLDEIGTAFSLYKTDEDISAYLAGKLSQPVLNALLENLSFDK
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KGILPNKAATQYKDEEDWEVMDNSATFKFSLHPNDLVKLVTKKKTILGYFNGLNRATG
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Figure 28

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TATGAATGGGCGGCCGTTTTATTGCATTTGGTGAAGCATCGCGGTTATTTATCGCAACGCAAAAGCGA
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TCAAAAACAACGTGAATTAGGCAATCCATTCACTTCACCAGAATTGGAACGGCAAGTTGATGATTTGT
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Figure 29

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KK*

Figure 30


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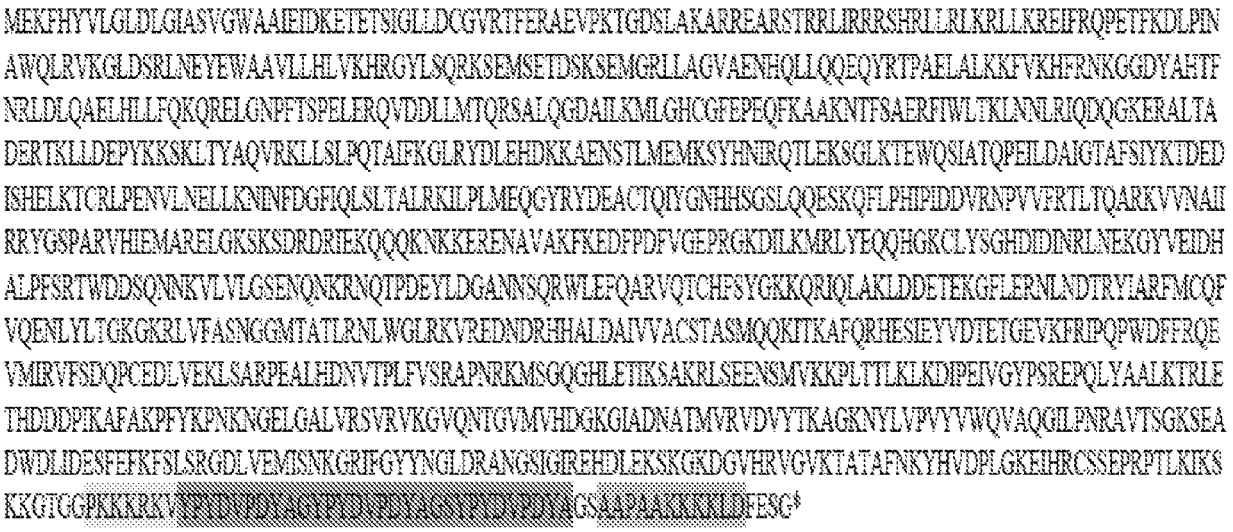
Figure 31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RRYGSPARVHIEMARELGKSKSDRDRIEKQQQKNKKERENAVAKFKEDFPDFVGEPRGKDILKMRLYEQQHGKCLYSGHDIDINRLNEKGYVEIDH
ALPFSRTWDDSQNNKVLVLGSENQNKRNQTPDEYLDGANNSQRWLEFQARVQTCHFSYGKKQRIQLAKLDDETEKGFLERNLNDTRYIARFMCQF
VQENLYLTGKGKRLVFASNGGMTATLRNLWGLRKVREDNDRHHALDAIVVACSTASMQQKITKAFQRHESIEYVDTETGEVKFRIPQPWDFFRQE
VMIRVFSDQPCEDLVEKLSARPEALHDNVTPLFVSRAPNRKMSGQGHLETIKSAKRLSEENSMVKKPLTTLKLKDIPEIVGYPSREPQLYAALKTRLE
THDDDPIKAFAKPFYKPNKNGELGALVRSVRVKGVQNTGVMVHDGKGIADNATMVRVDVYTKAGKNYLVPVYVWQVAQGILPNRAVTSGKSEA
DWDLIDESFEFKFSLSRGDLVEMISNKGRIFGYYNGLDRANGSIGIREHDLEKSKGKDGVHRVGVKTATAFNKYHVDPLGKEIHRCSSEPRPTLKIKS
KKGTGGPKKKRKV

Figure 32

Nme2 sgRNA:



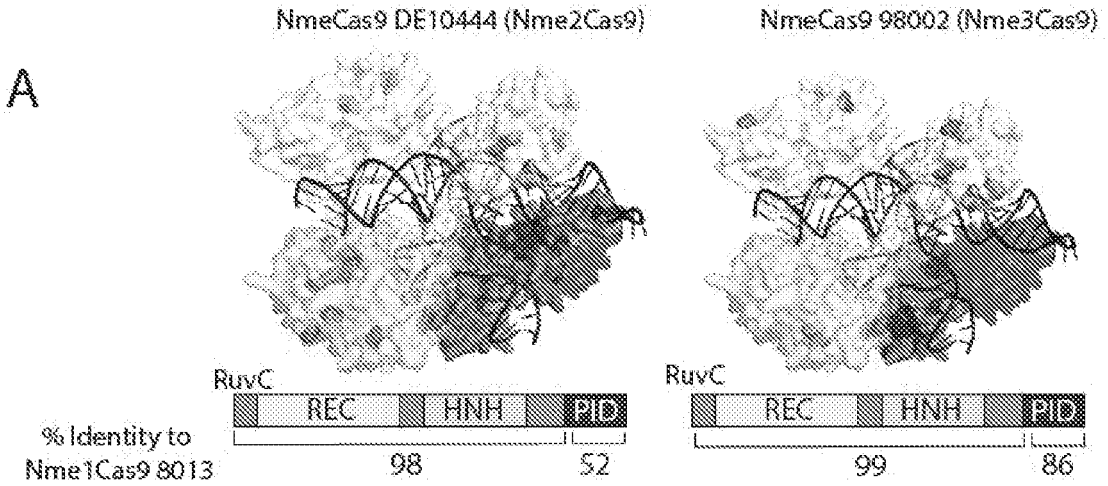
Hpa sgRNA:



Smu sgRNA:



Figure 33


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

A

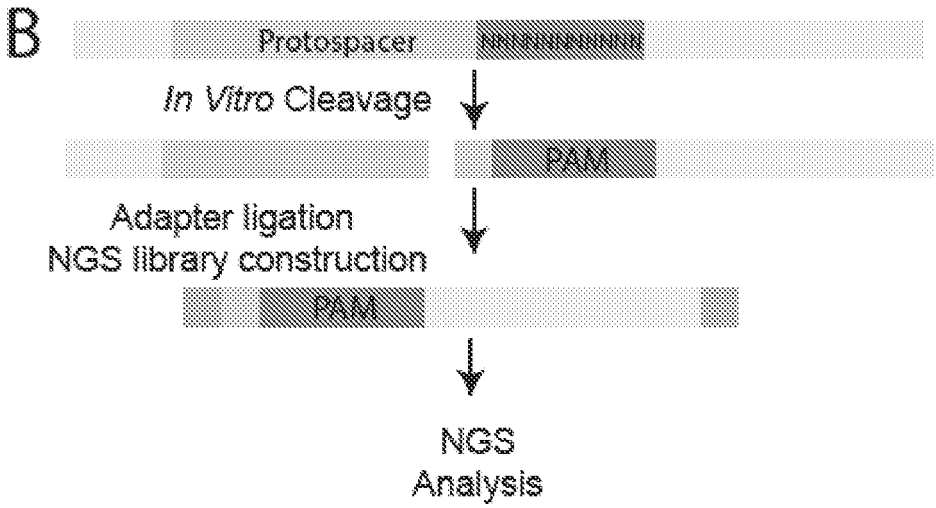

B
Protospacer
In Vitro Cleavage
PAM
Adapter ligation
NGS library construction
PAM
NGS
Analysis

Figure 34

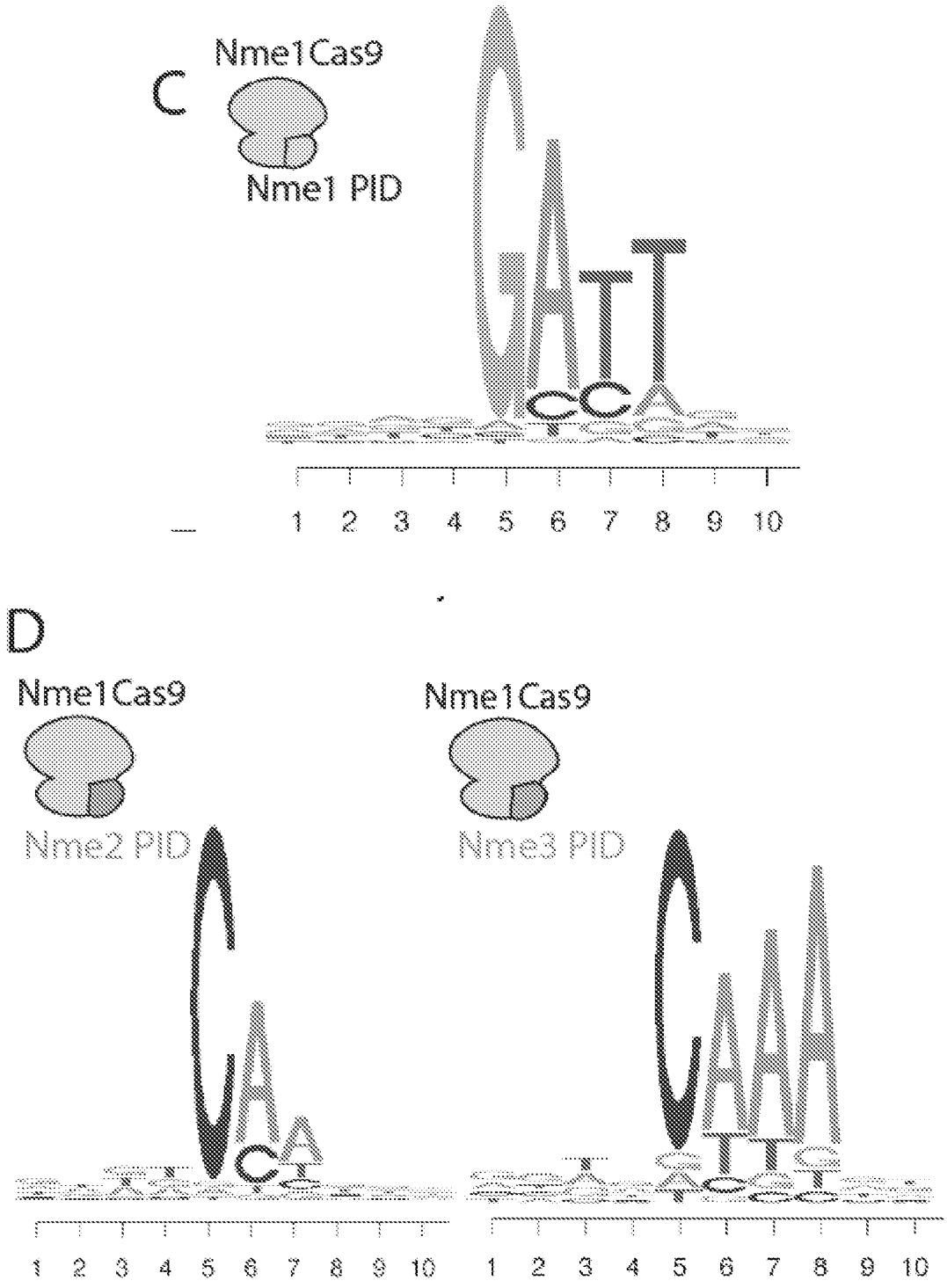


Figure 34 (cont'd)

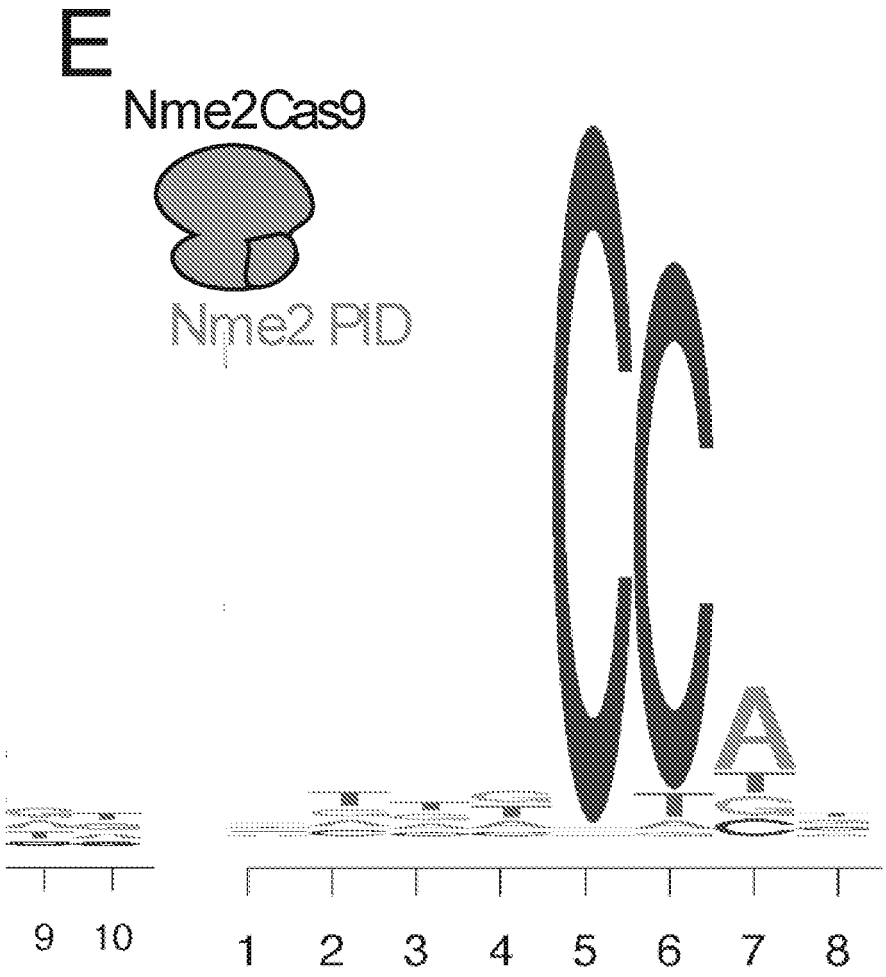


Figure 34 (cont'd)

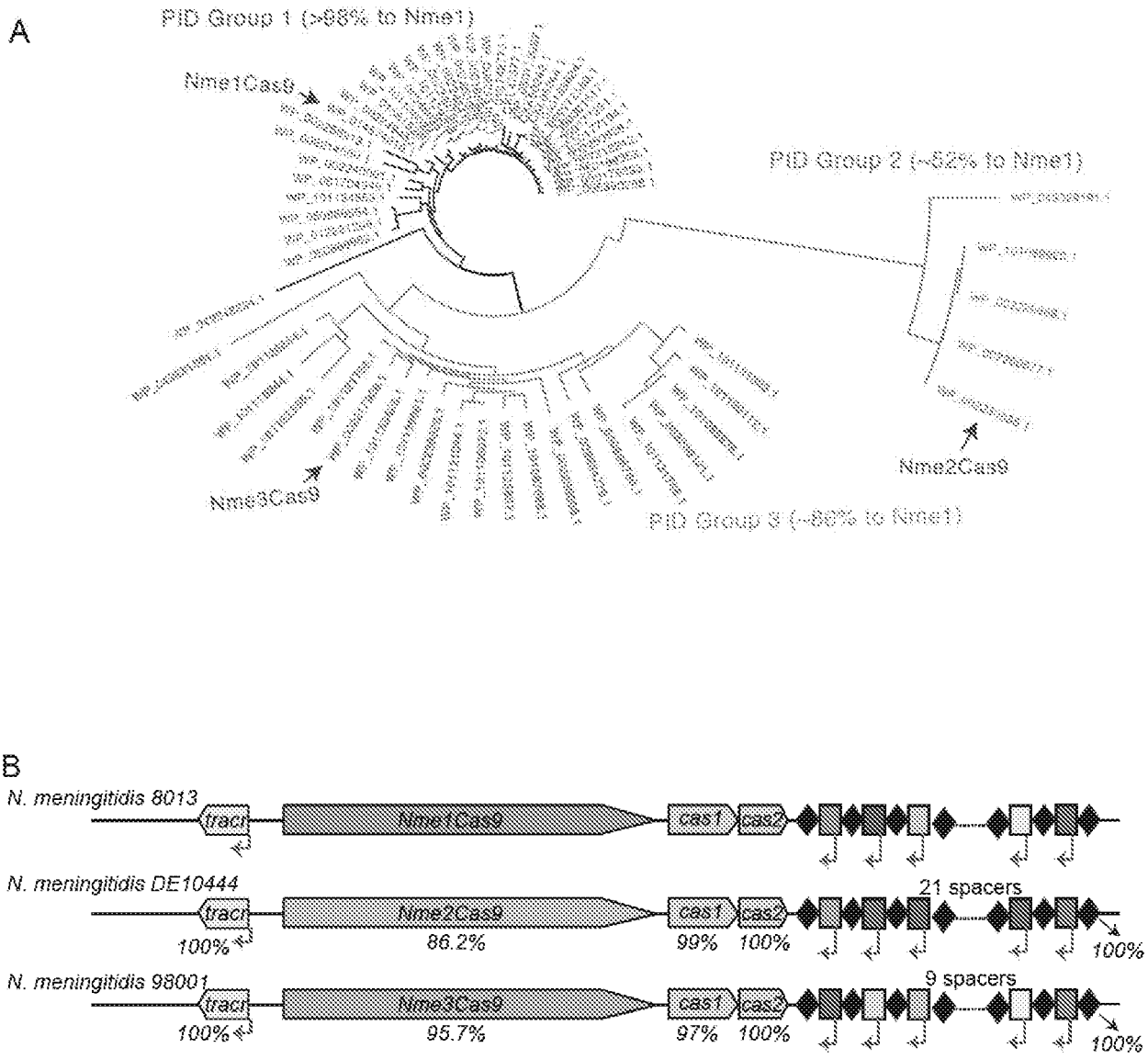

A
PID Group 1 (>98% to Nme1)
Nme1Cas9
PID Group 2 (~62% to Nme1)
Nme2Cas9
Nme3Cas9
PID Group 3 (~80% to Nme1)
B
N. meningitidis 8013
tracr
Nme1Cas9
cas1
cas2
N. meningitidis DE10444
21 spacers
tracr
Nme2Cas9
cas1
cas2
100%
86.2%
99%
100%
100%
N. meningitidis 98001
9 spacers
tracr
Nme3Cas9
cas1
cas2
100%
95.7%
97%
100%
100%

Figure 35

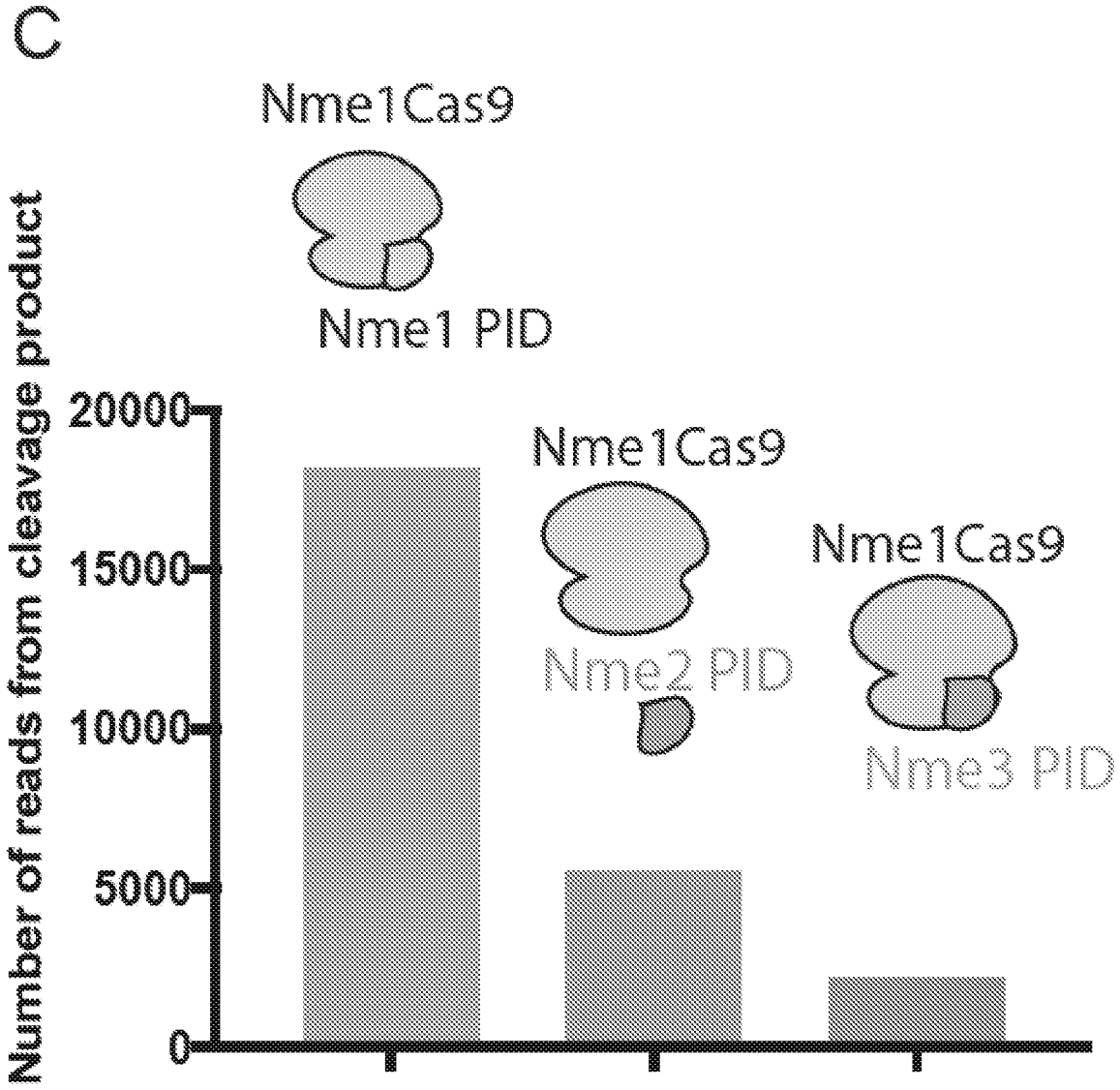


Figure 35 (cont'd)

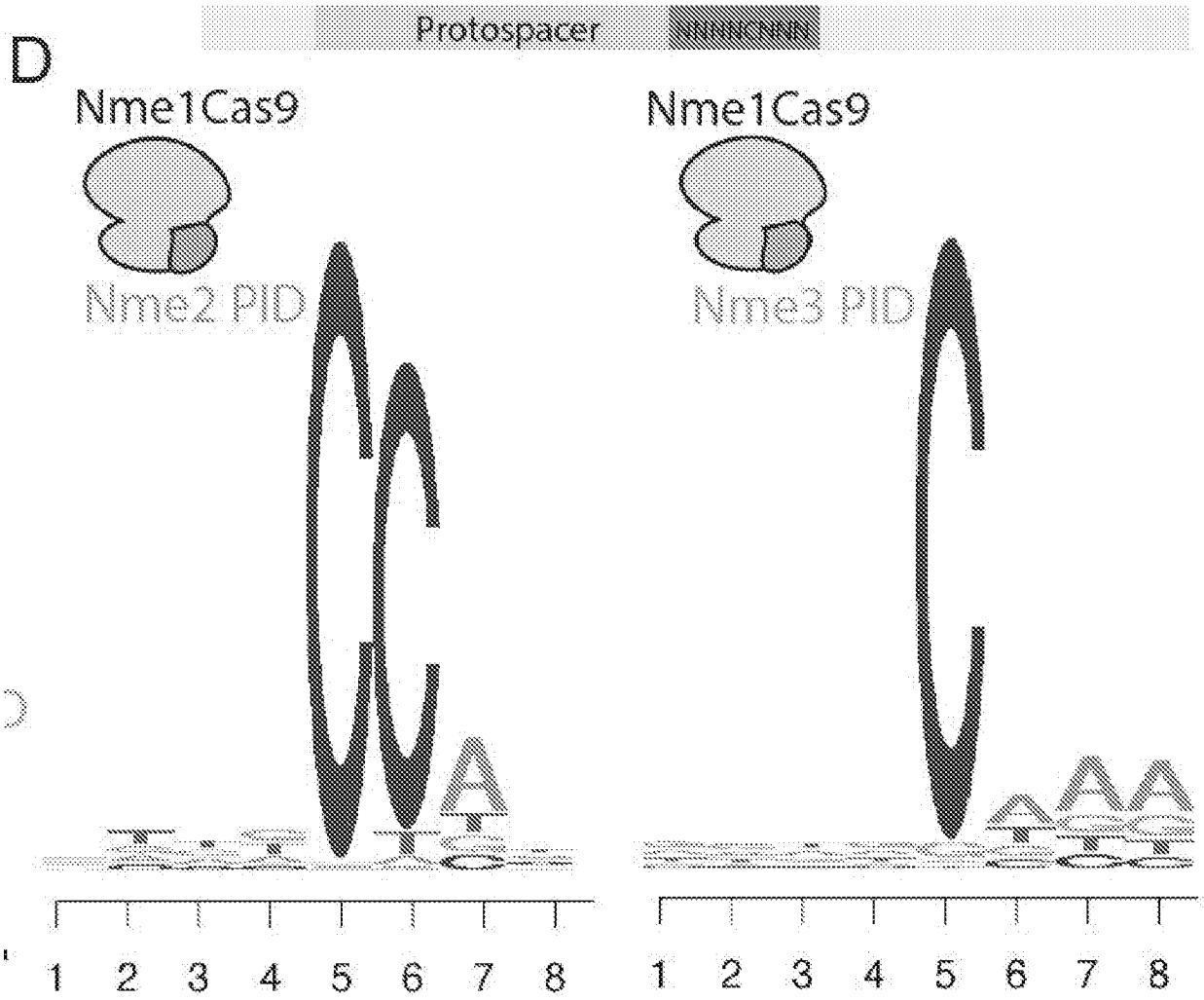


Figure 35 (cont'd)

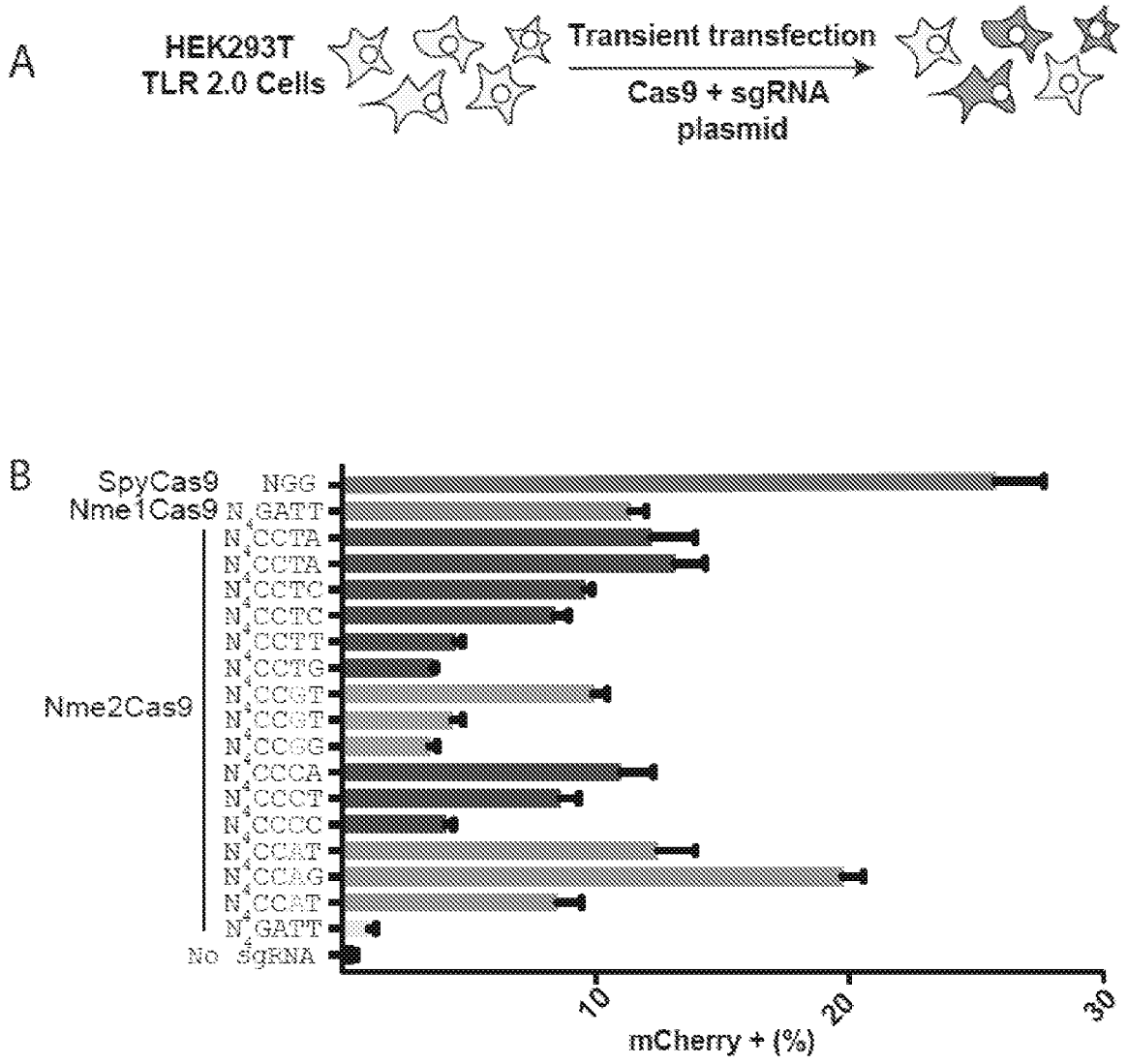
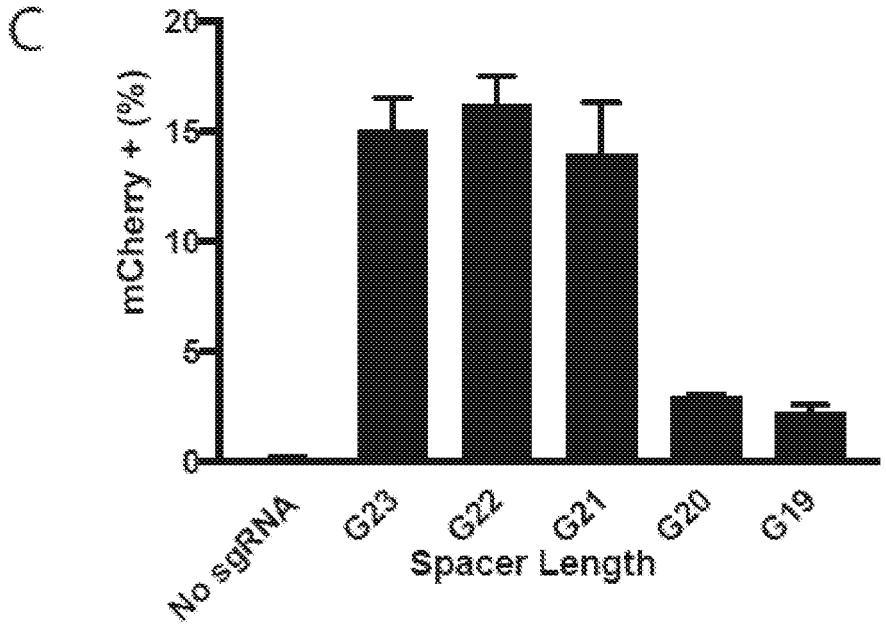

A
HEK293T
TLR 2.0 Cells
Transient transfection
Cas9 + sgRNA
plasmid
B
SpyCas9
Nme1Cas9
Nme2Cas9
NGG
N4GATT
N4CCTA
N4CCTA
N4CCTC
N4CCTC
N4CCTT
N4CCTG
N4CCGT
N4CCGT
N4CCGG
N4CCCA
N4CCCT
N4CCCC
N4CCAT
N4CCAG
N4CCAT
N4GATT
No sgRNA
10
20
30
mCherry + (%)

Figure 36



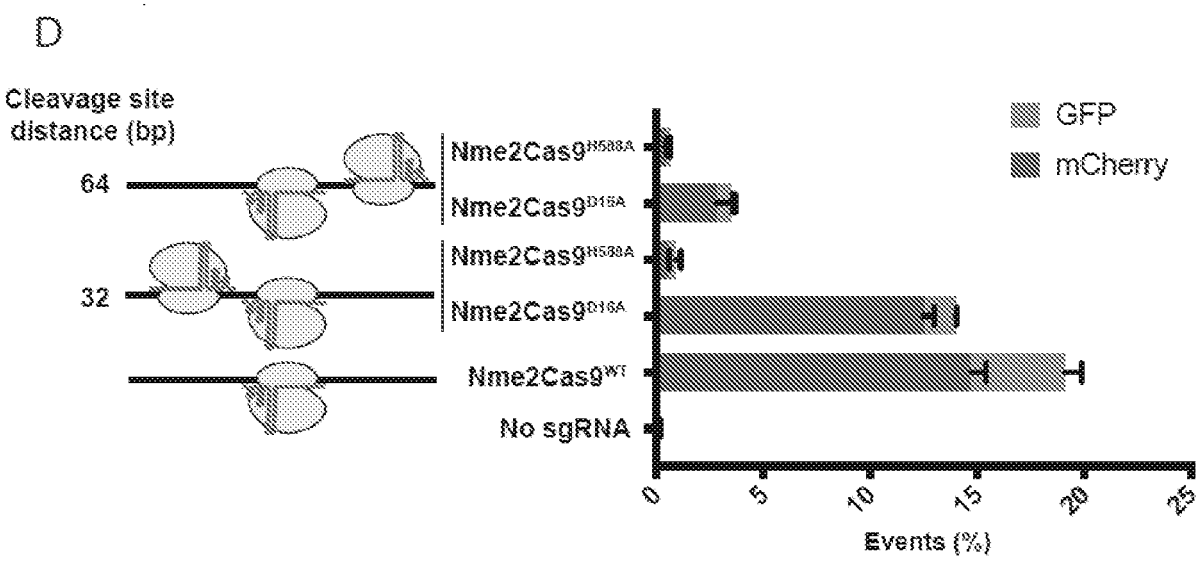


Figure 36 (cont'd)

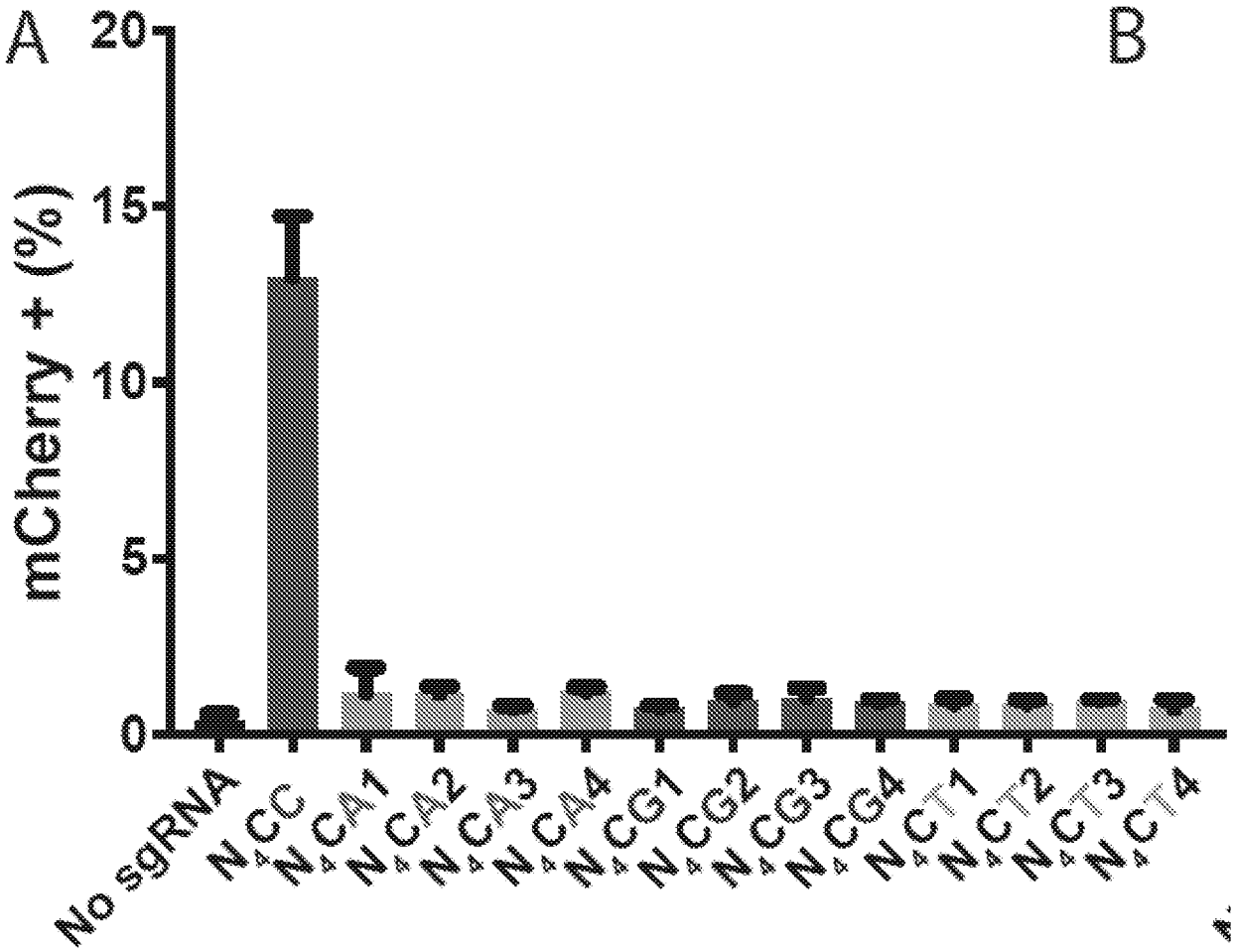

A
B
20
15
10
5
0
mCherry + (%)
No sgRNA
NΔCC
NΔCA1
NΔCA2
NΔCA3
NΔCA4
NΔCG1
NΔCG2
NΔCG3
NΔCG4
NΔCT1
NΔCT2
NΔCT3
NΔCT4

Figure 37

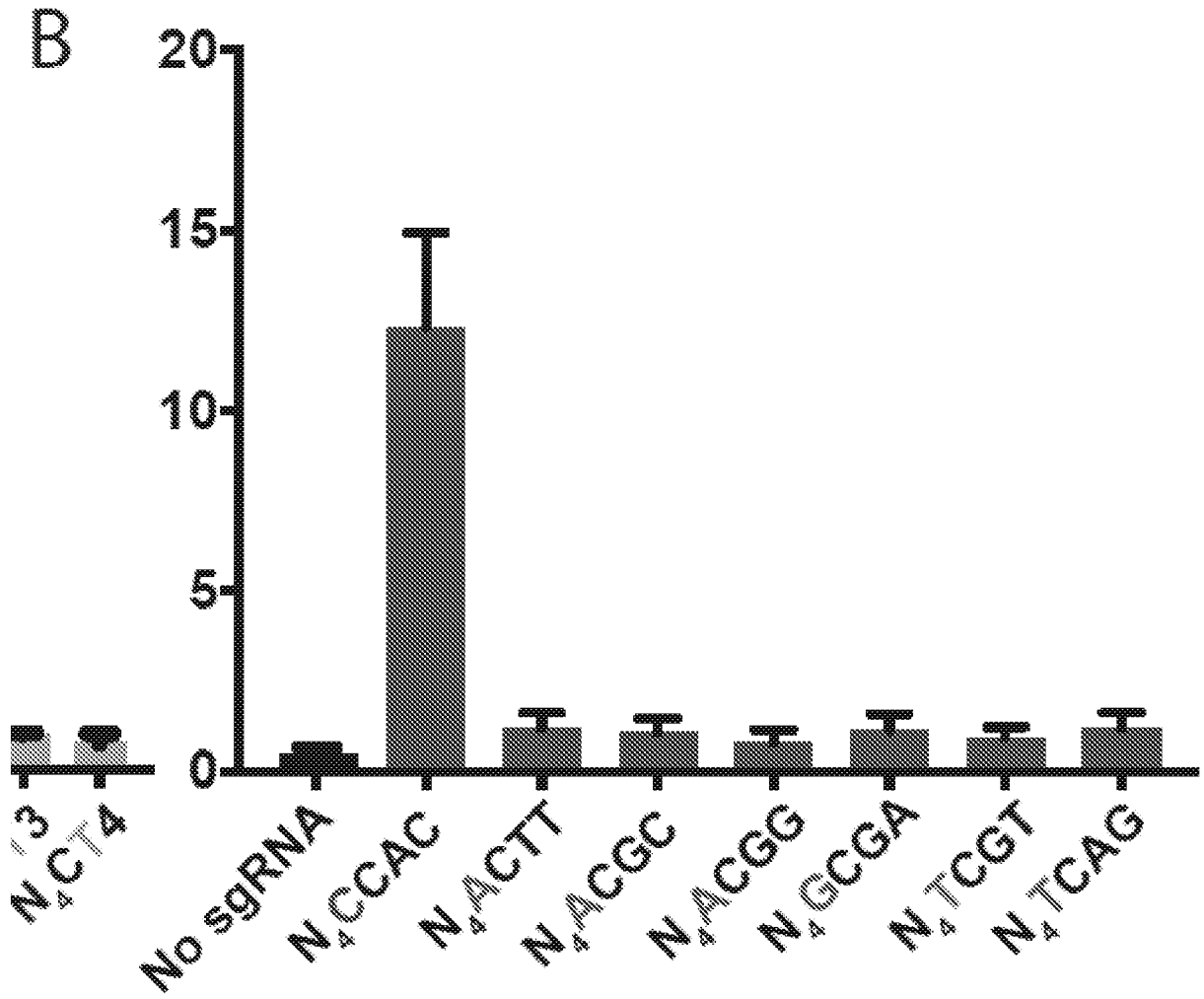


Figure 37 (cont'd)

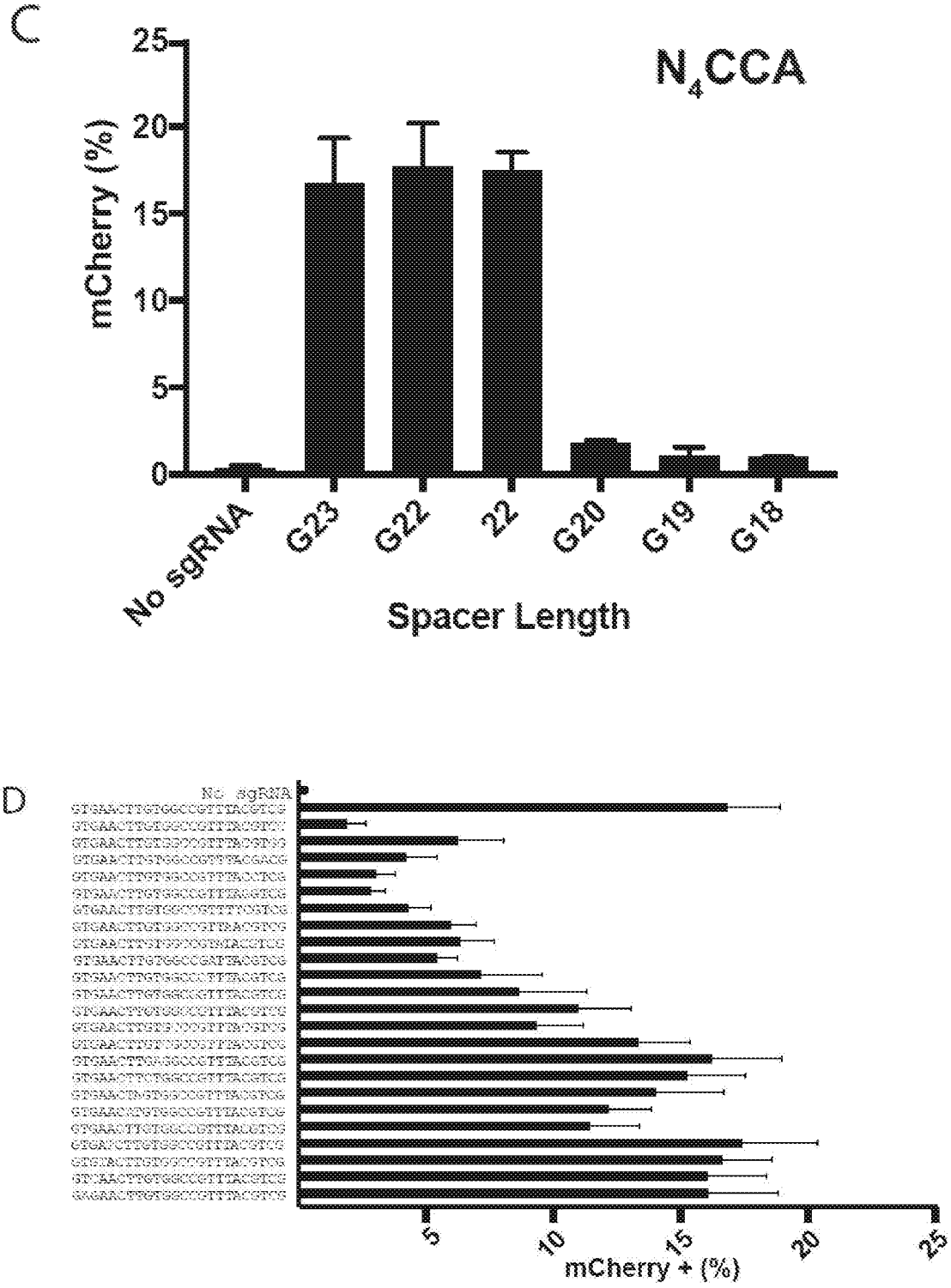


Figure 37 (cont'd)

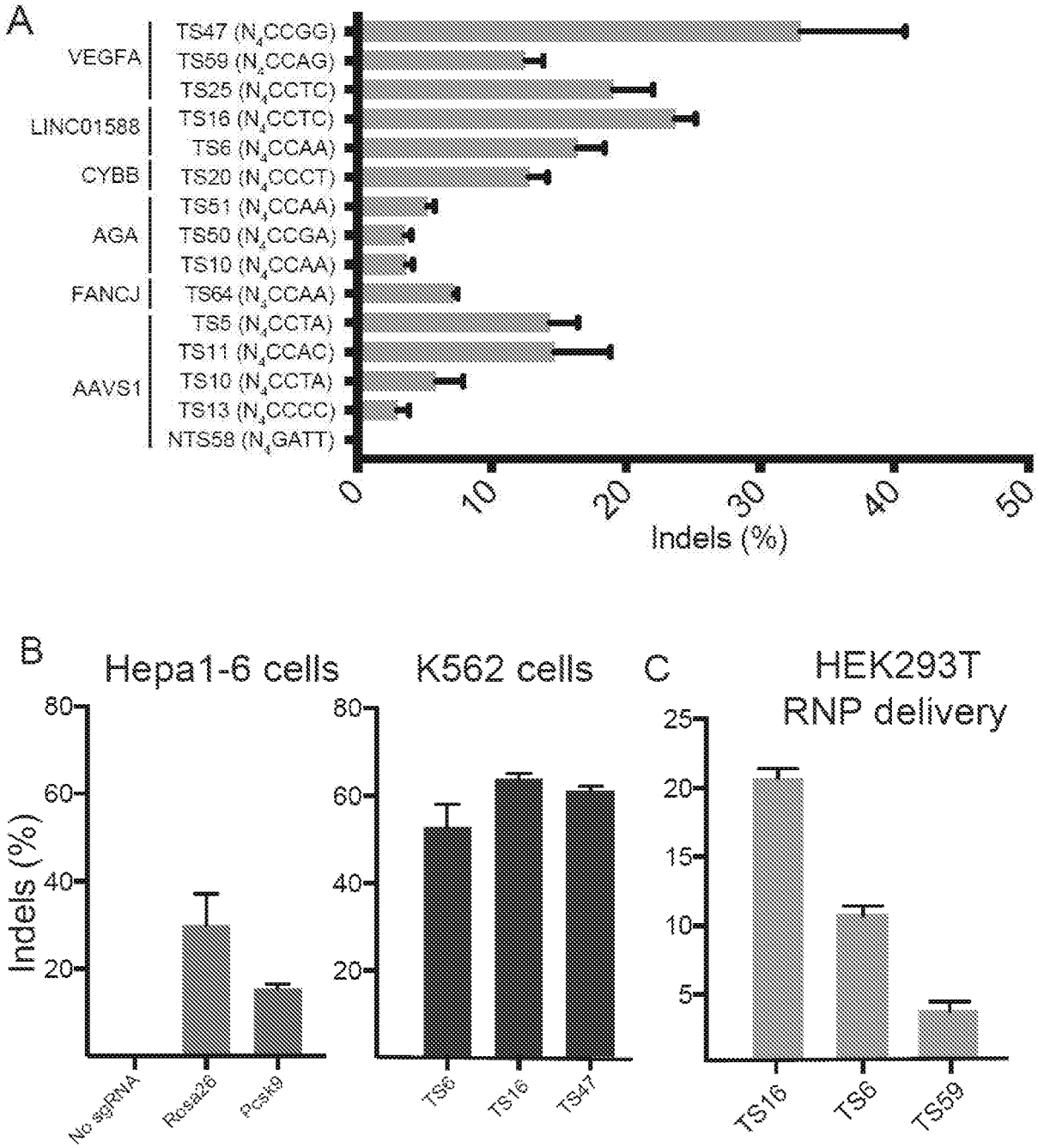

A
VEGFA
LINC01588
CYBB
AGA
FANCJ
AAVS1
TS47 (N4CCGG)
TS59 (N2CCAG)
TS25 (N4CCTC)
TS16 (N4CCTC)
TS6 (N4CCAA)
TS20 (N4CCCT)
TS51 (N4CCAA)
TS50 (N4CCGA)
TS10 (N4CCAA)
TS64 (N4CCAA)
TS5 (N4CCTA)
TS11 (N4CCAC)
TS10 (N4CCTA)
TS13 (N4CCCC)
NTS58 (N4GATT)
0
10
20
30
40
50
Indels (%)
B
Hepa1-6 cells
K562 cells
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

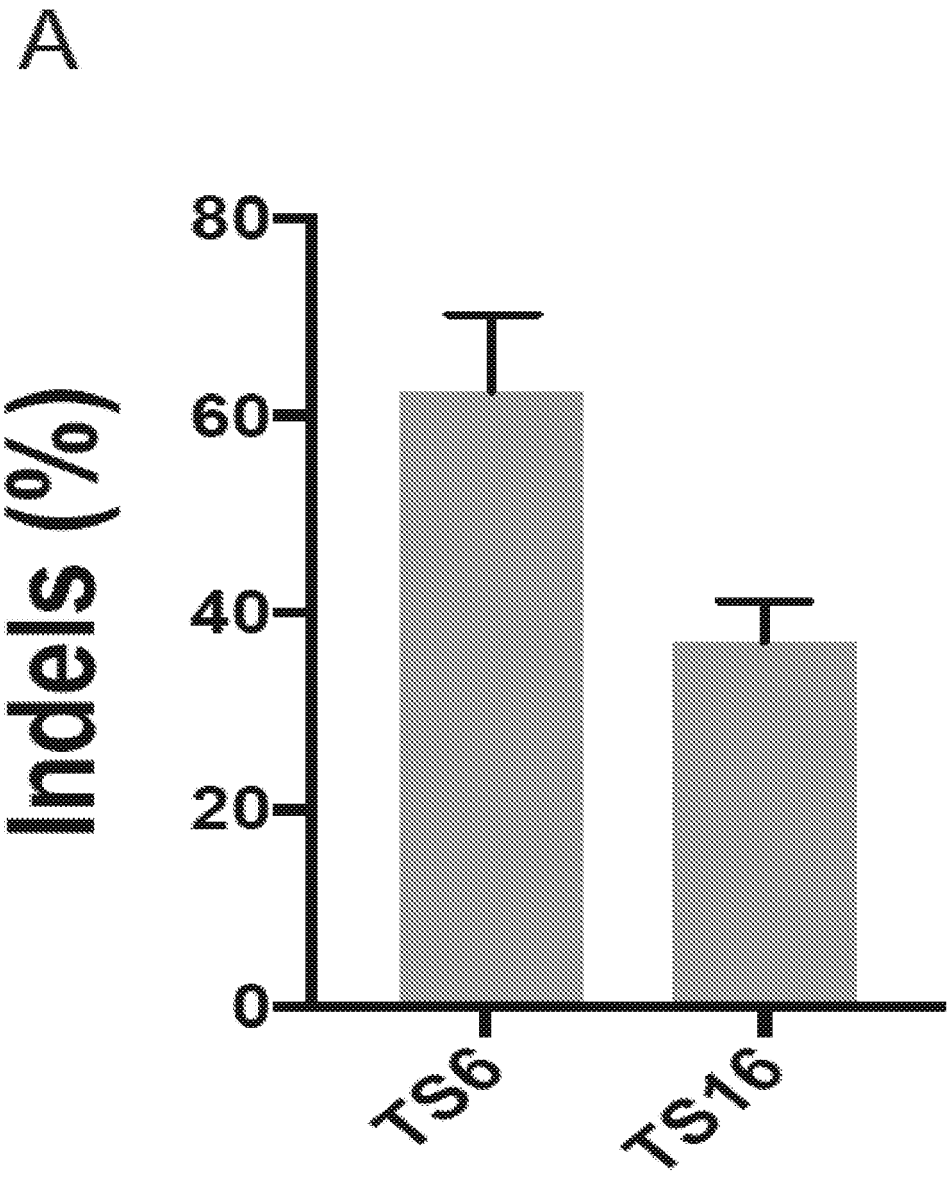


Figure 39

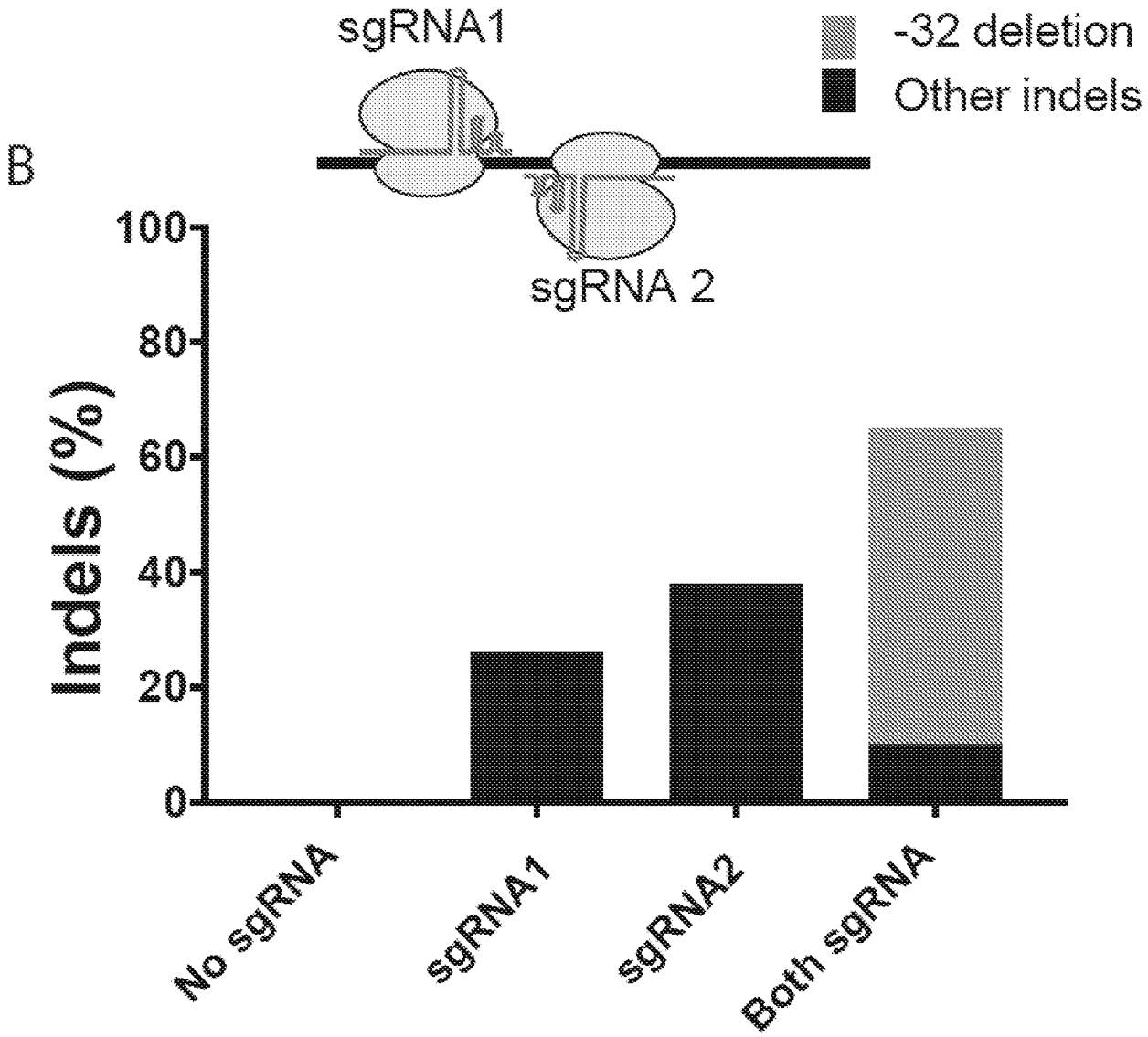


Figure 39 (cont'd)

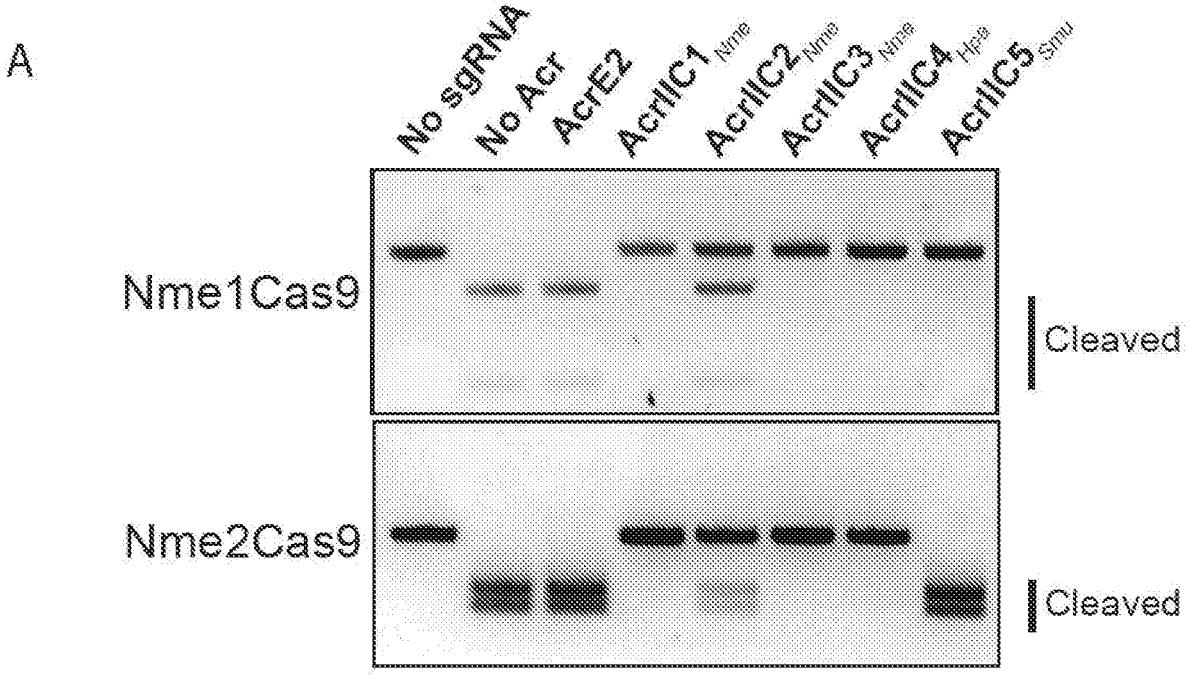

A
No sgRNA
No Acr
AcrE2
AcrIIC1 Nme
AcrIIC2 Nme
AcrIIC3 Nme
AcrIIC4 Hpa
AcrIIC5 Smu
Nme1Cas9
Cleaved
Nme2Cas9
Cleaved

Figure 40

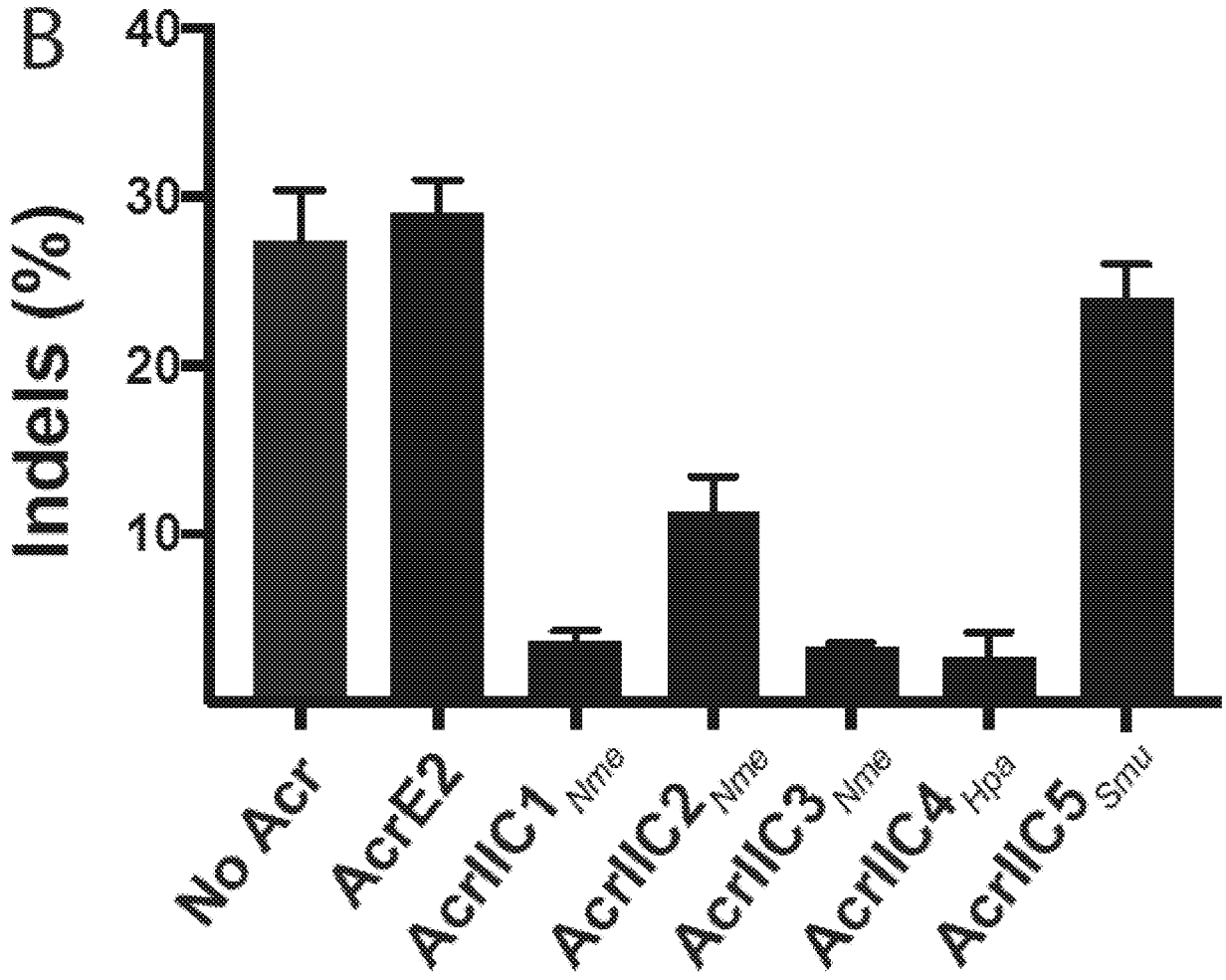


Figure 40 (cont'd)

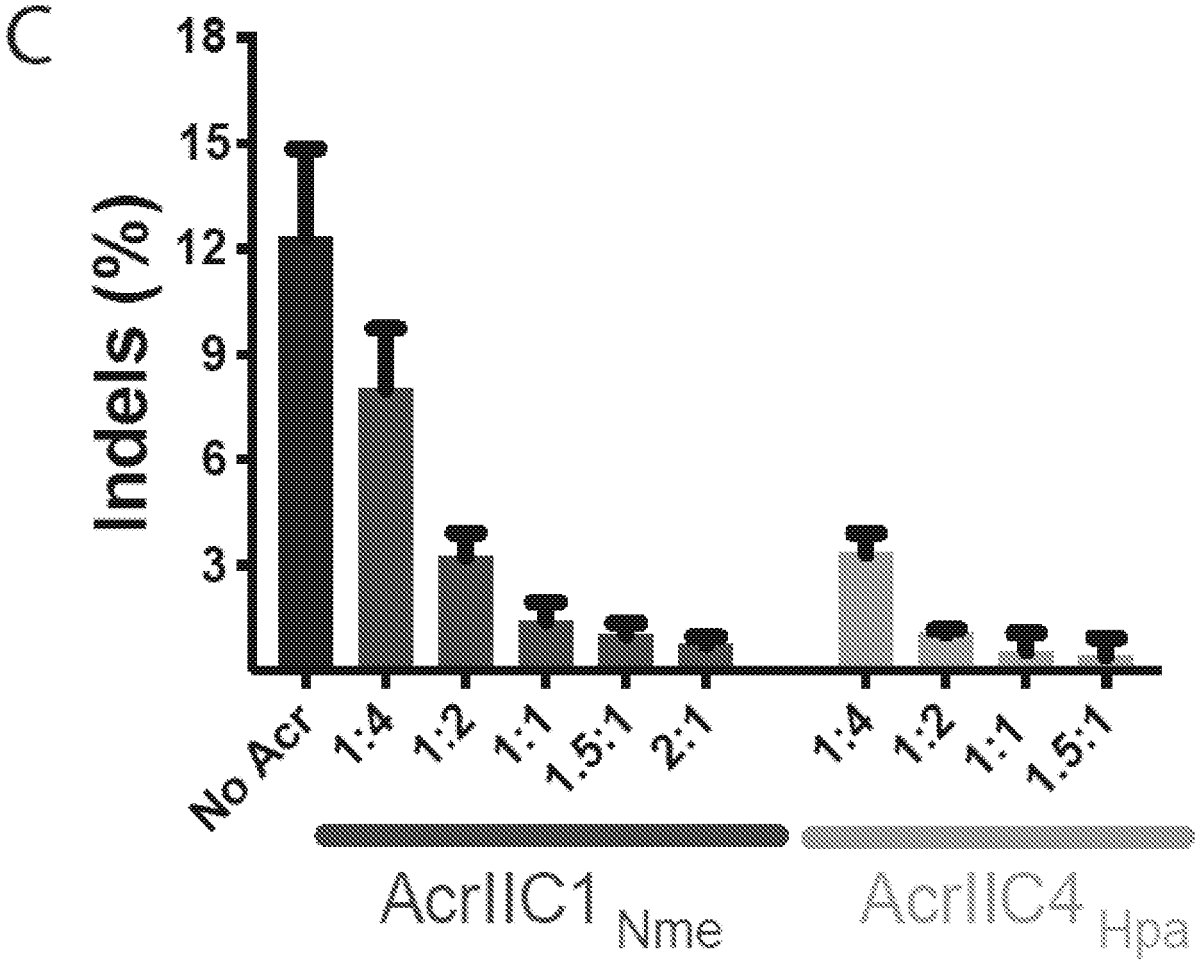


Figure 40 (cont'd)

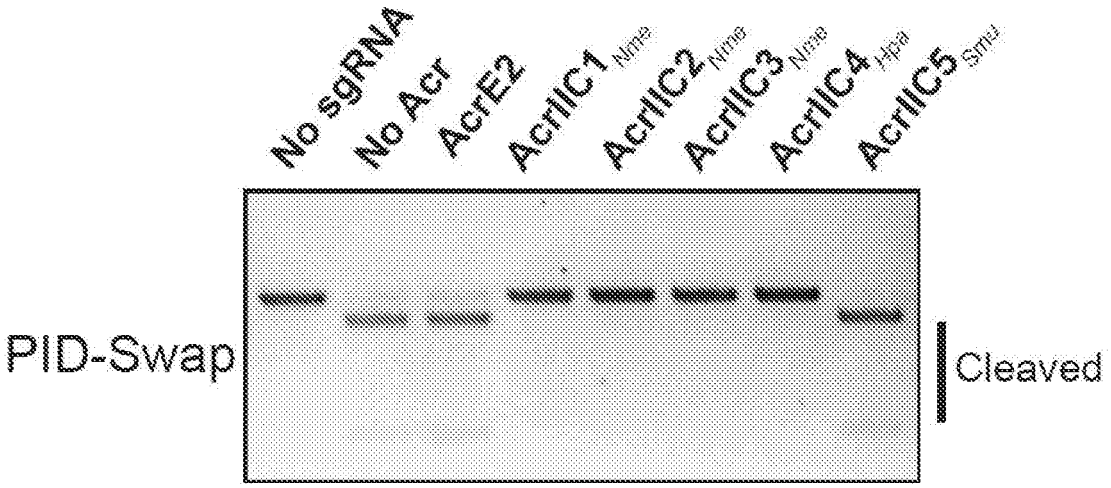

No sgRNA
No Acr
AcrE2
AcrIIC1 Nme
AcrIIC2 Nme
AcrIIC3 Nme
AcrIIC4 Hpa
AcrIIC5 Sma
PID-Swap
Cleaved

Figure 41

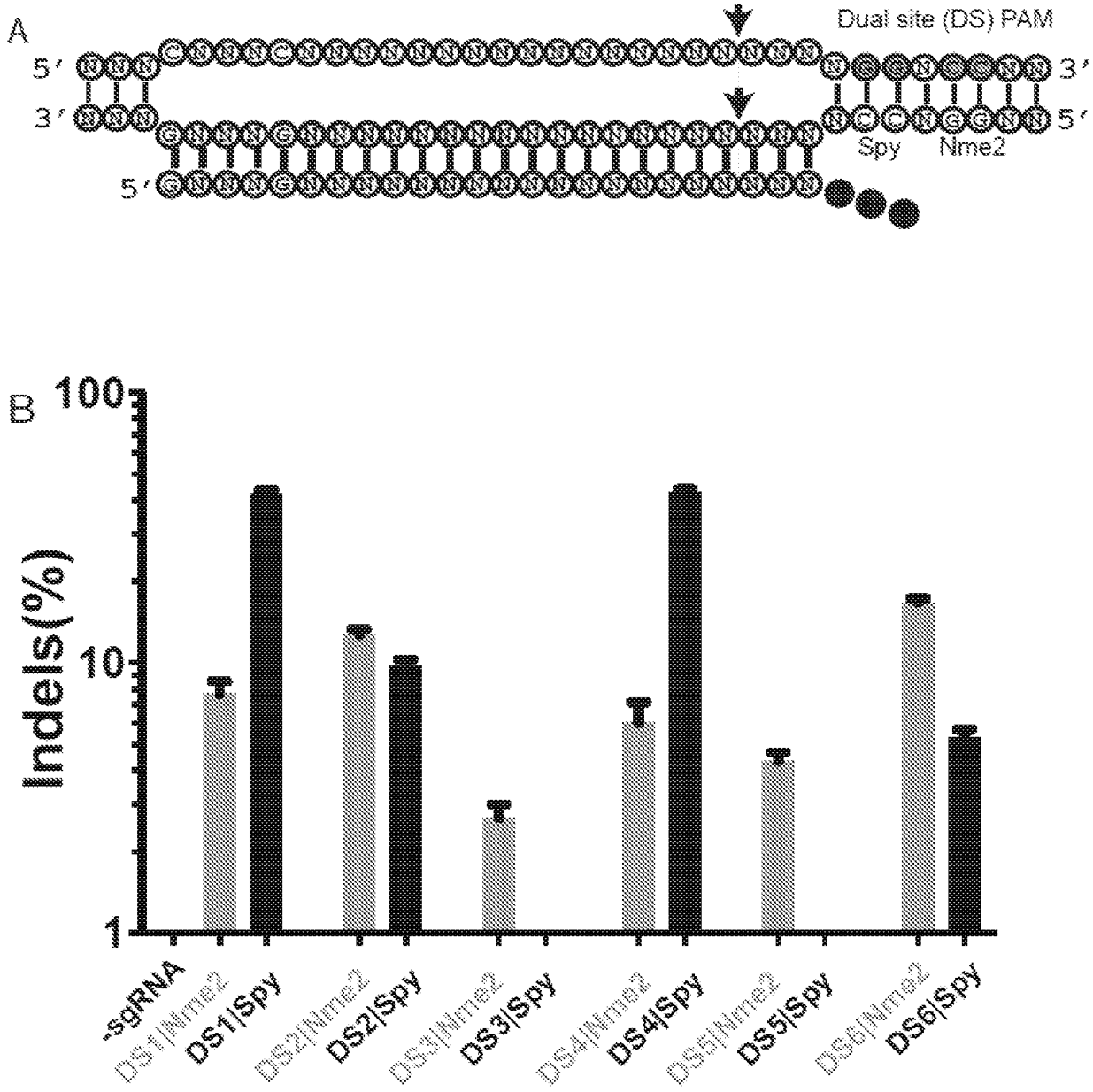

A
Dual site (DS) PAM
5′
3′
3′
5′
5′
Spy
Nme2
B
100
10
1
Indels(%)
-sgRNA
DS1|Nme2
DS1|Spy
DS2|Nme2
DS2|Spy
DS3|Nme2
DS3|Spy
DS4|Nme2
DS4|Spy
DS5|Nme2
DS5|Spy
DS6|Nme2
DS6|Spy

Figure 42

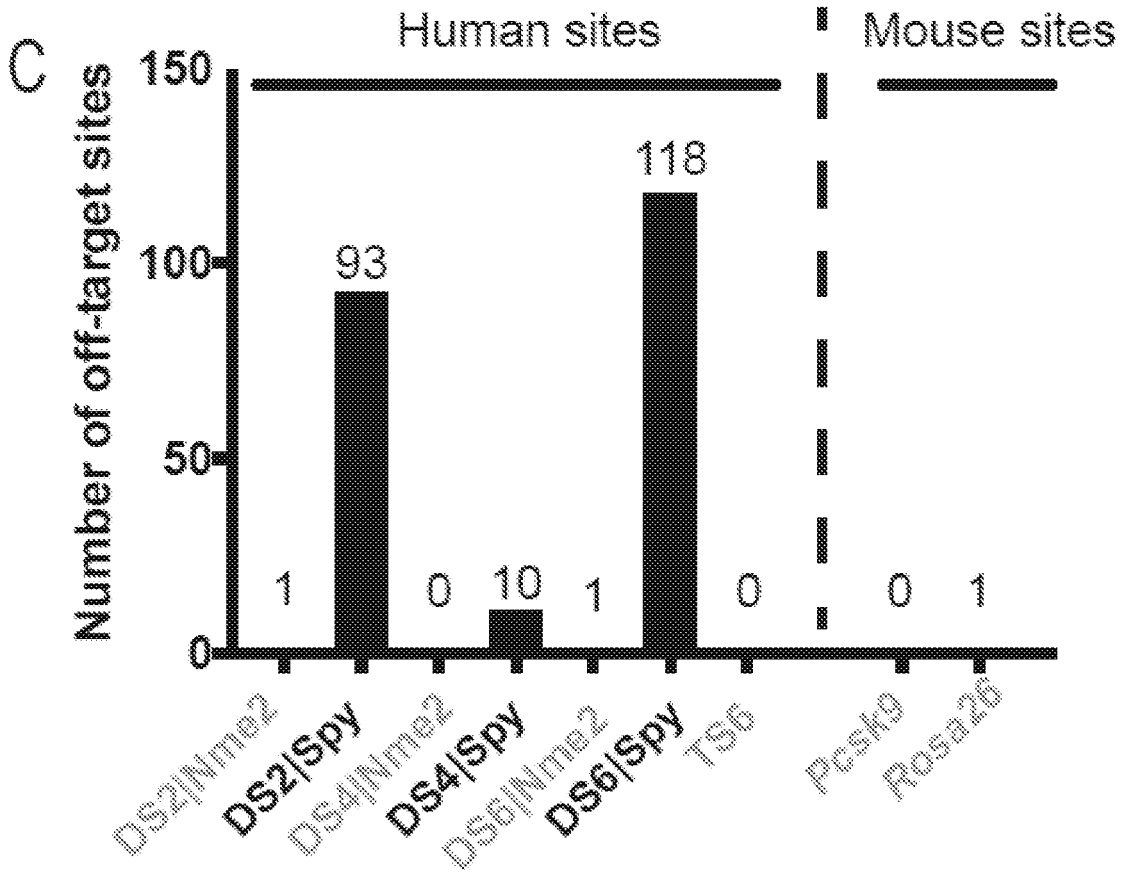


Figure 42 (cont'd)

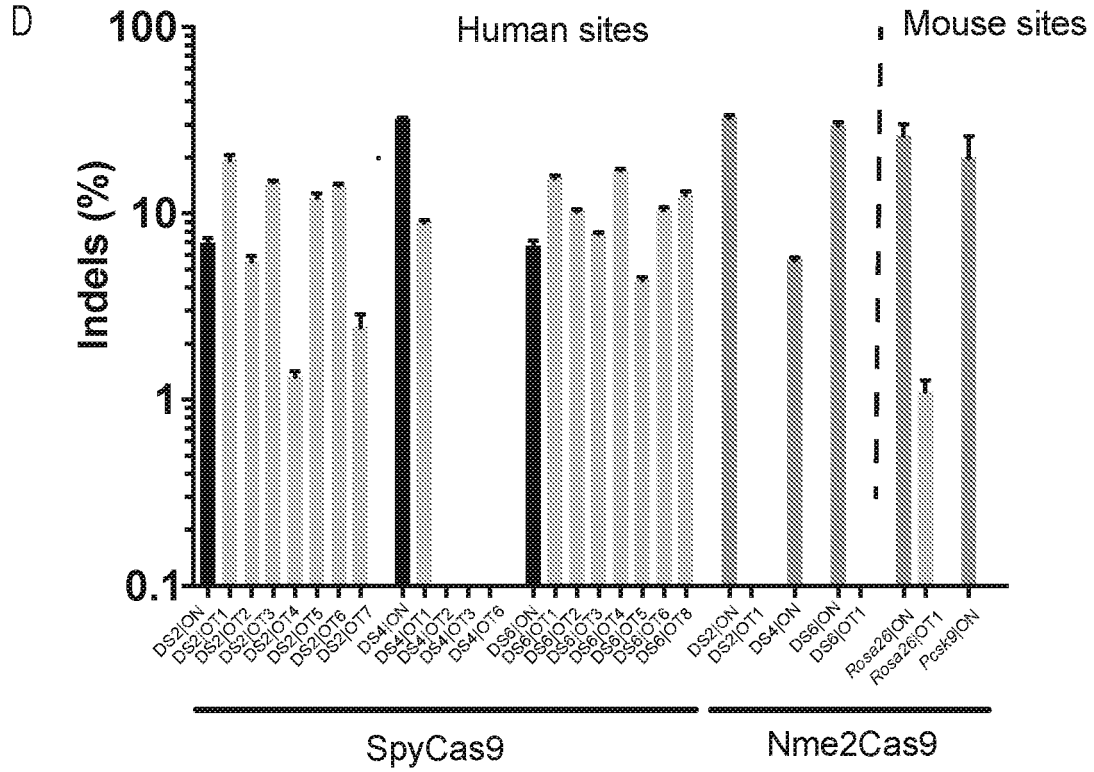


Figure 42 (cont'd)

Figure 42E

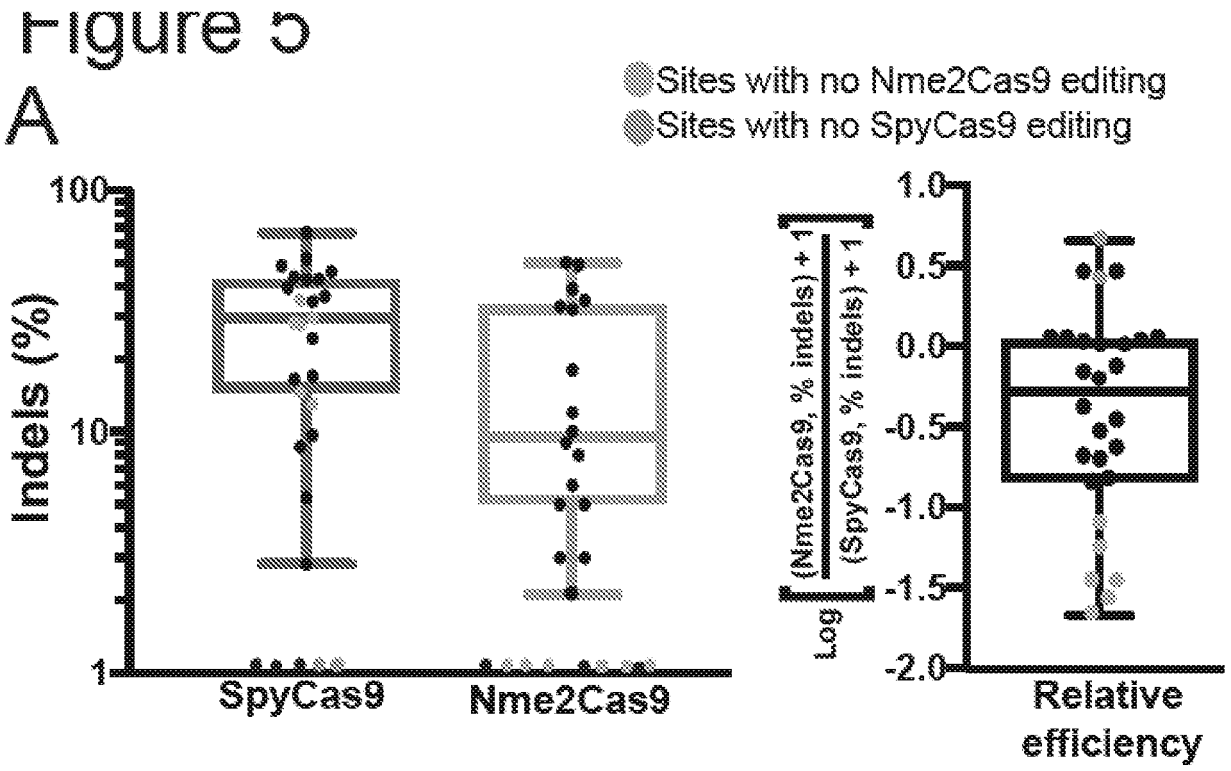


Figure 42F

Rosa26|On : TGAGGACCGCCCTGGGCCTGGGAGAATCCCT

Rosa26|OT1 : GAAGGACCACCCTAGGCCTGGGAGACTCCCT

Figure 42 (cont'd)

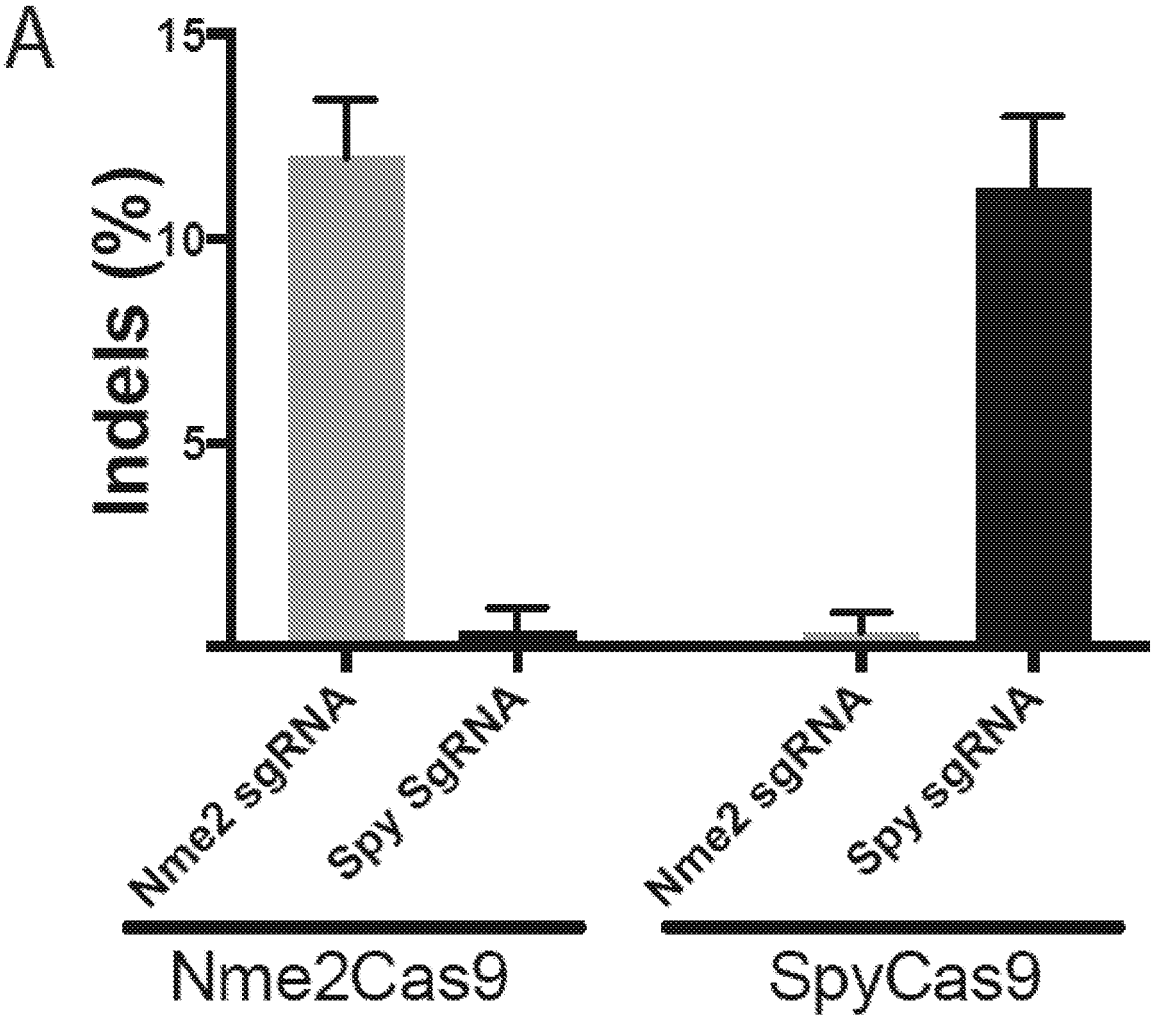

A
15
10
5
Indels (%)
Nme2 sgRNA
Spy sgRNA
Nme2 sgRNA
Spy sgRNA
Nme2Cas9
SpyCas9

Figure 43

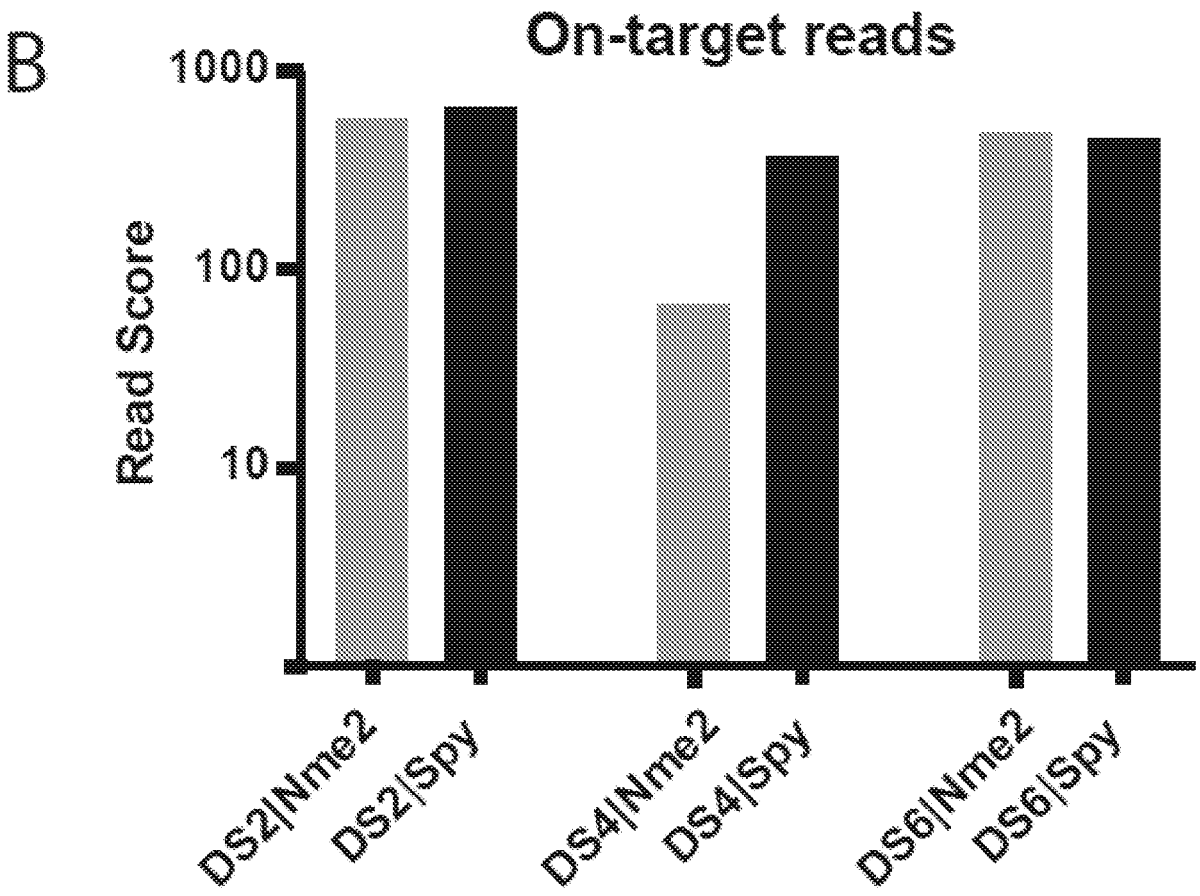


Figure 43 (cont'd)

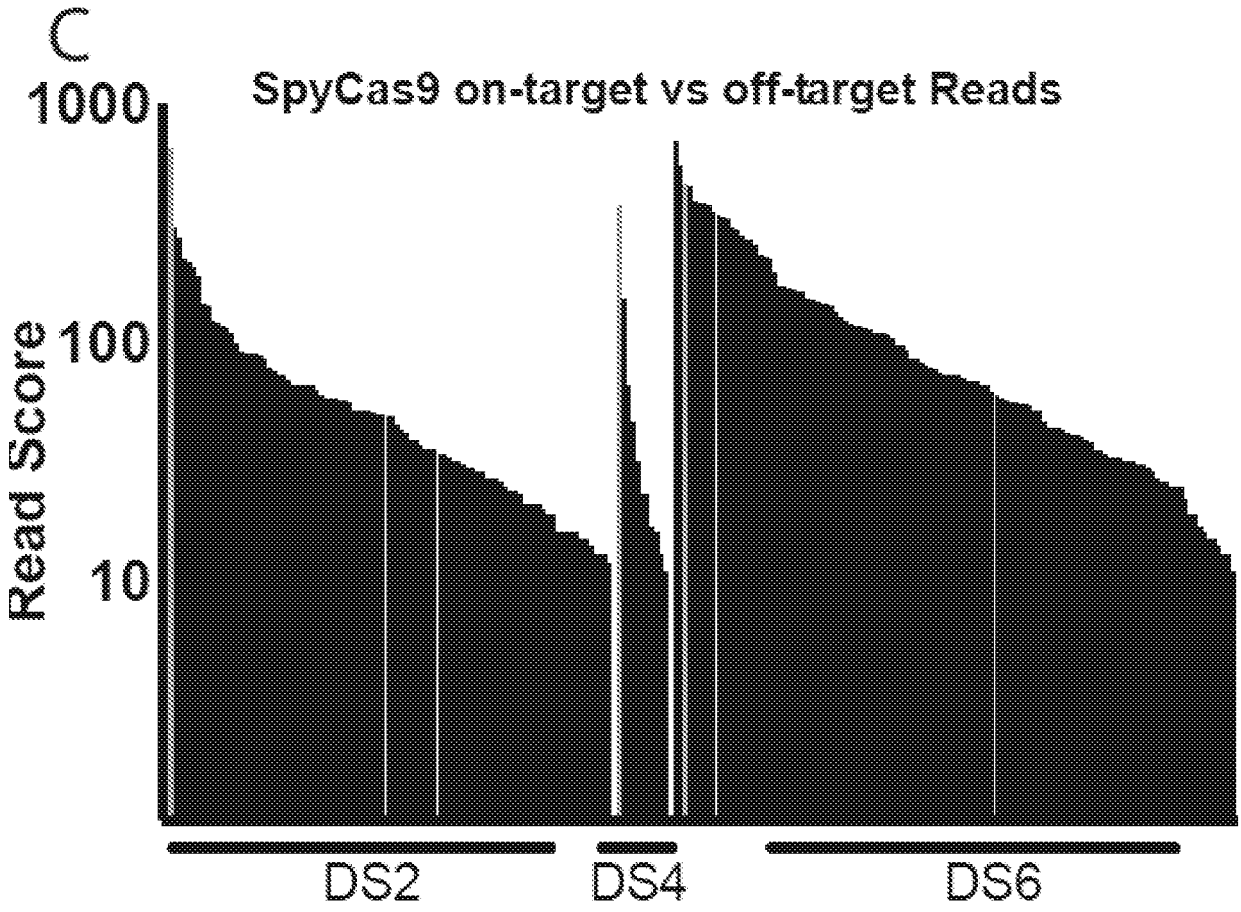


Figure 43 (cont'd)

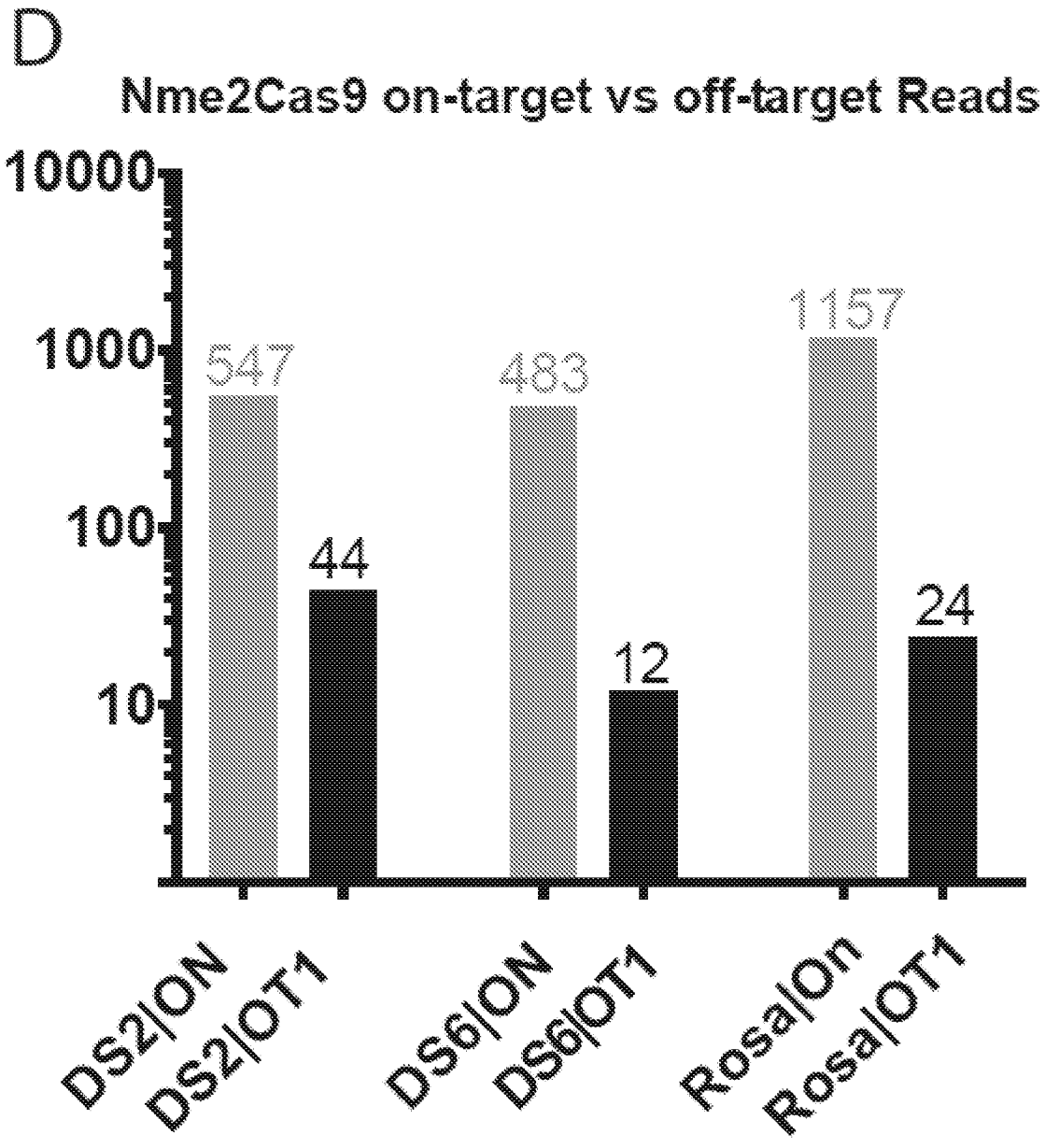


Figure 43 (cont'd)

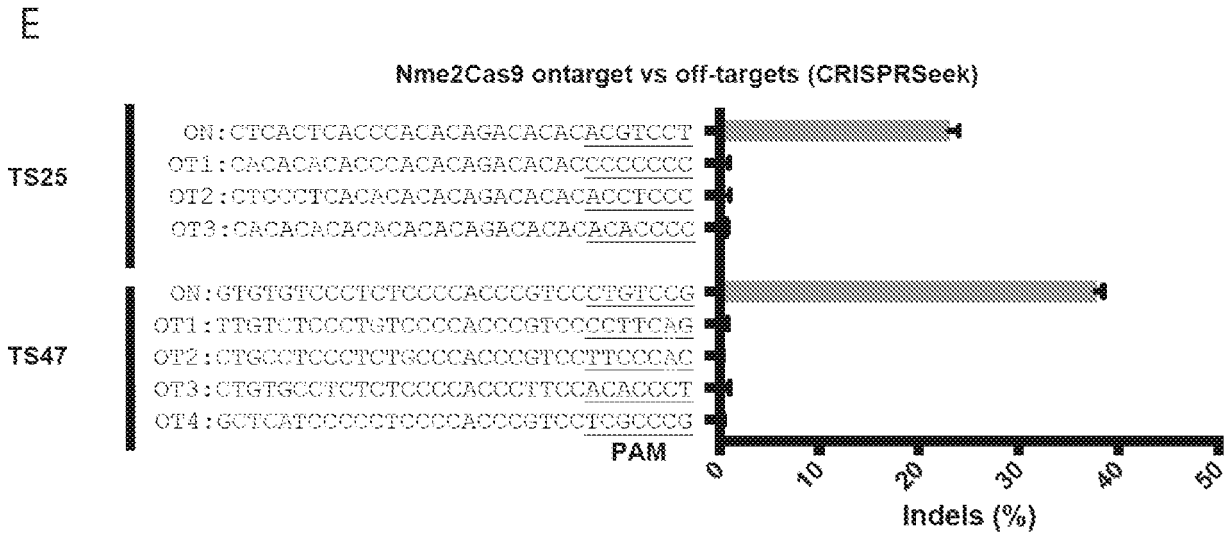
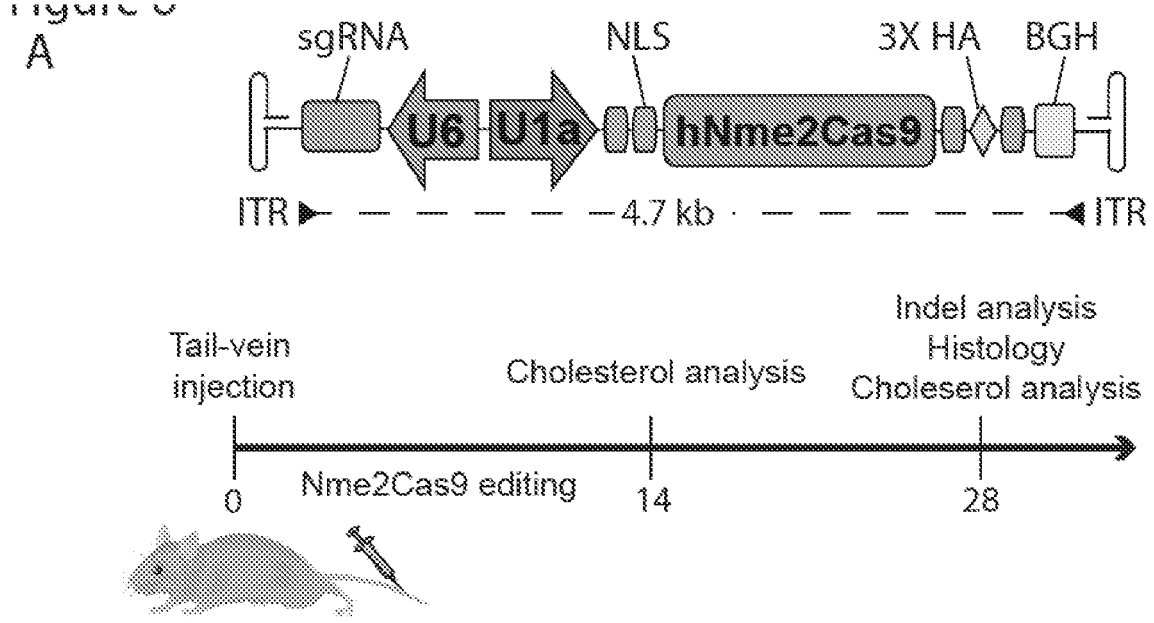


Figure 43 (cont'd)


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

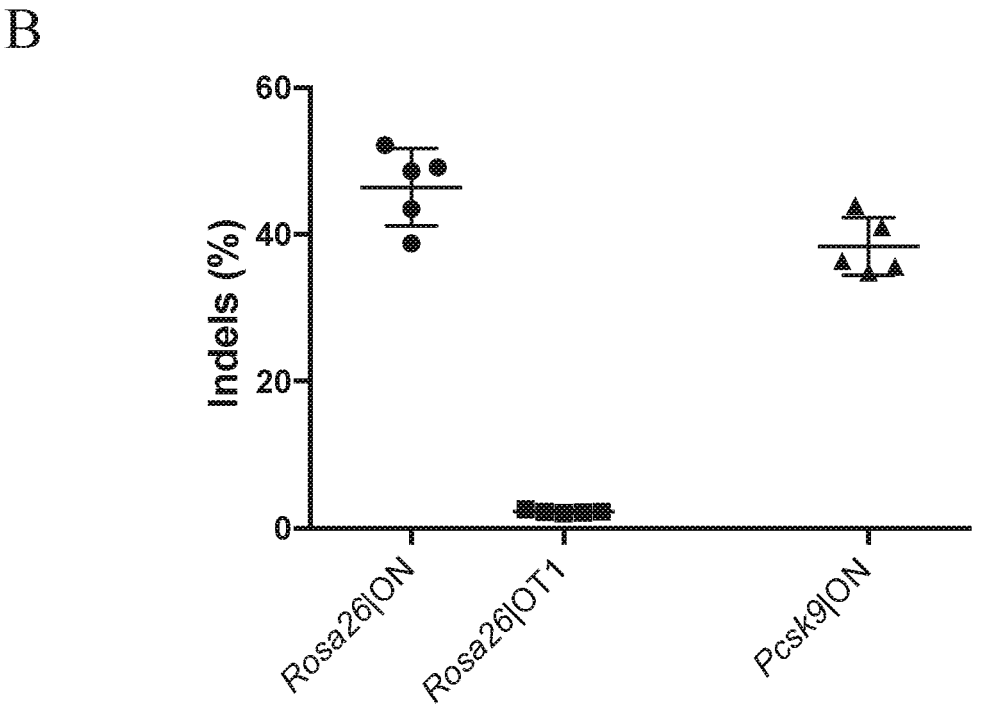
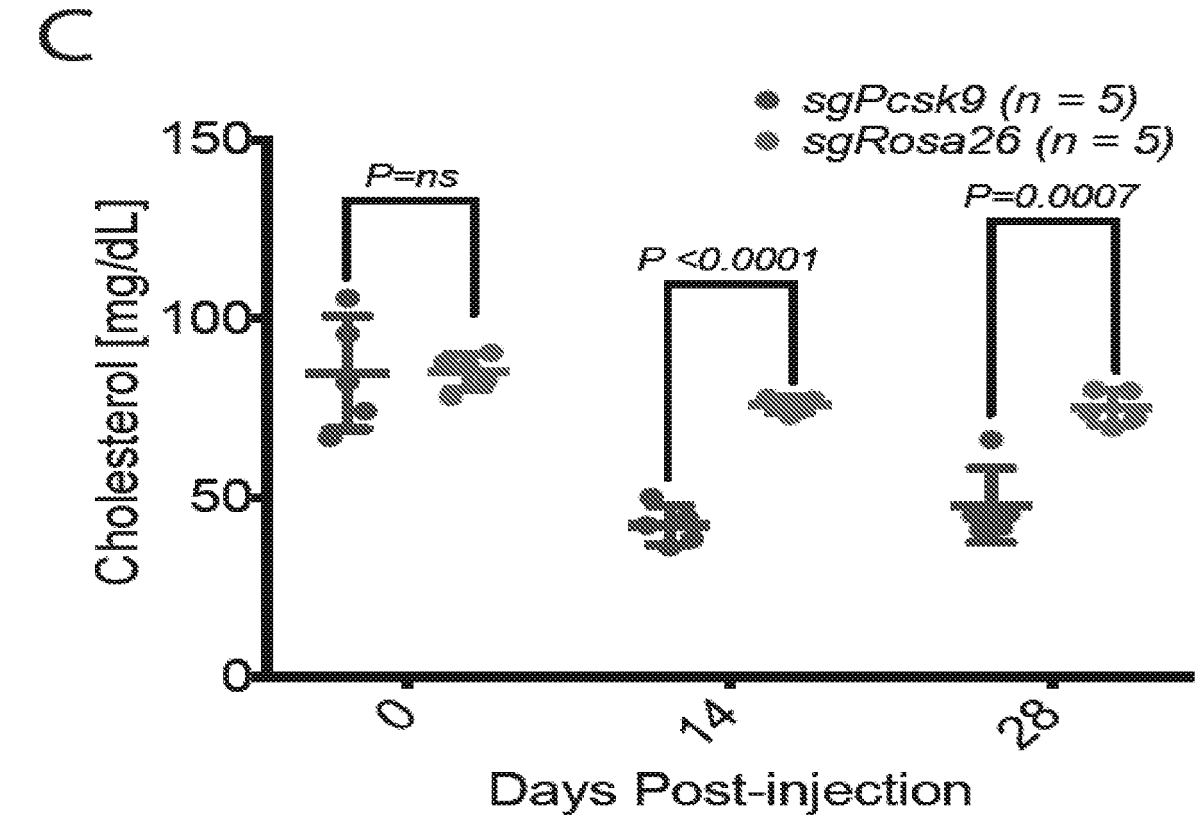

B
60
40
20
0
Indels (%)
Rosa26|ON
Rosa26|OT1
Pcsk9|ON

Figure 44



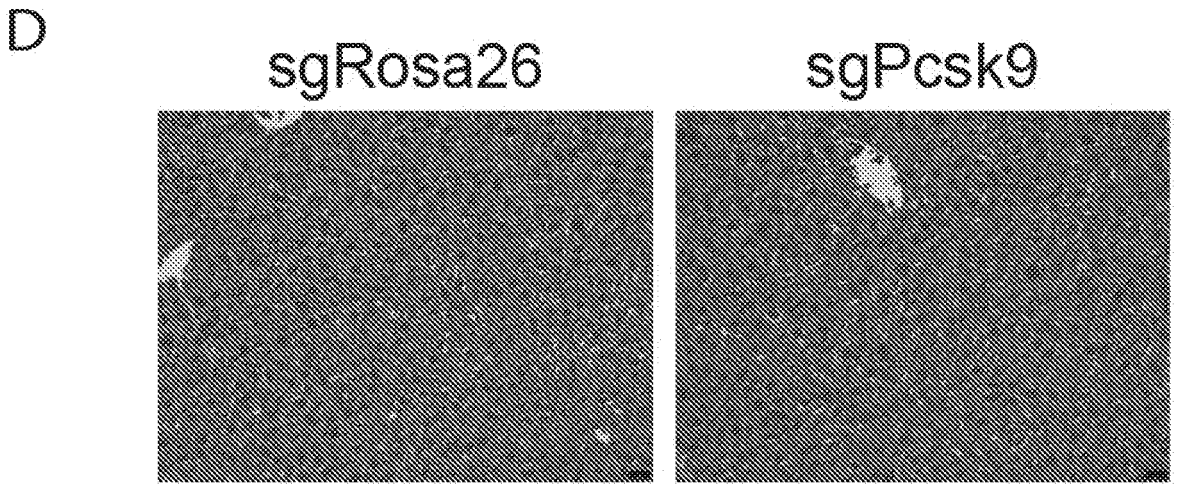


Figure 44 (cont'd)

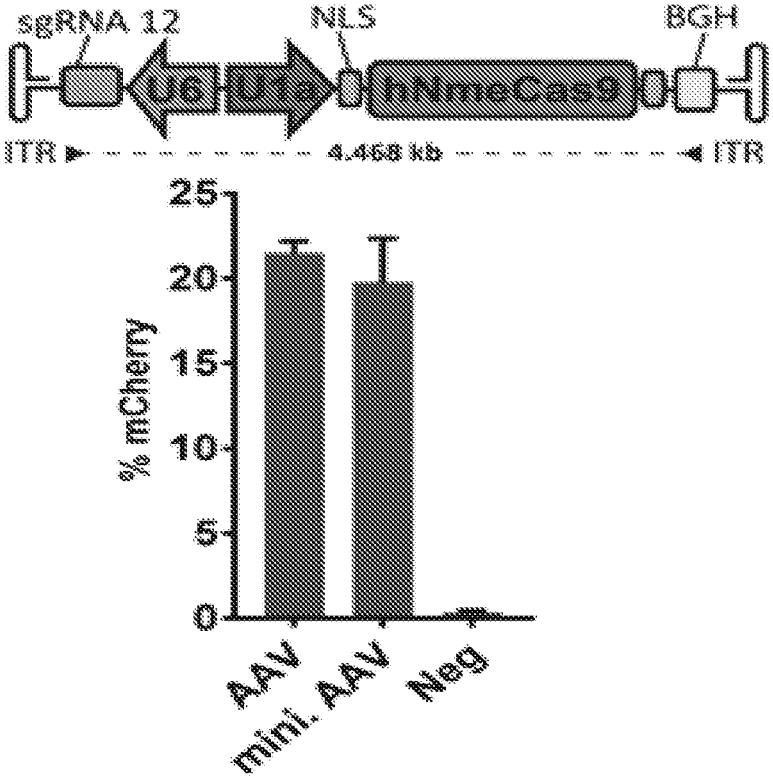

sgRNA 12
NLS
BGH
U6
U1a
hNmeCas9
ITR
4.468 kb
ITR
% mCherry
25
20
15
10
5
0
AAV
mini. AAV
Neg

Figure 45

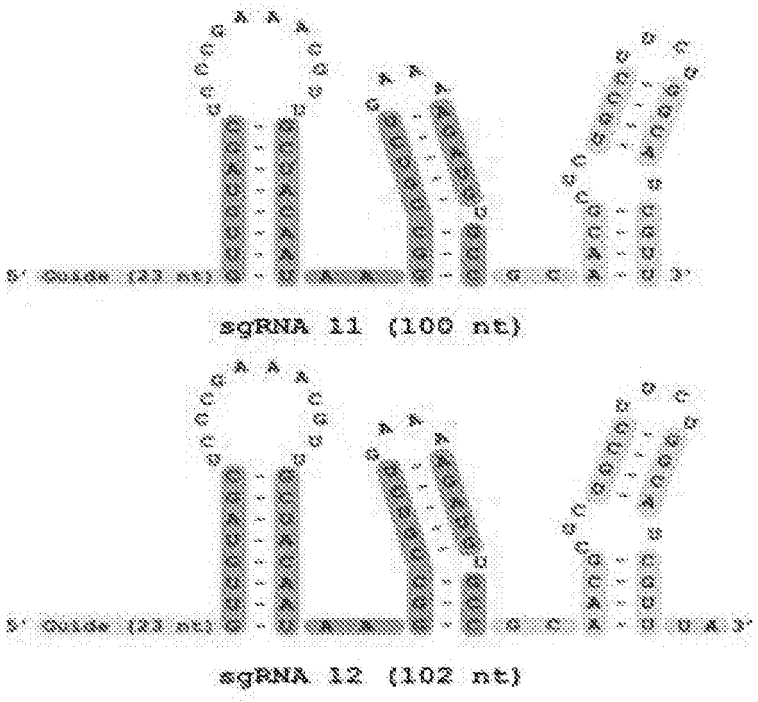


Figure 46

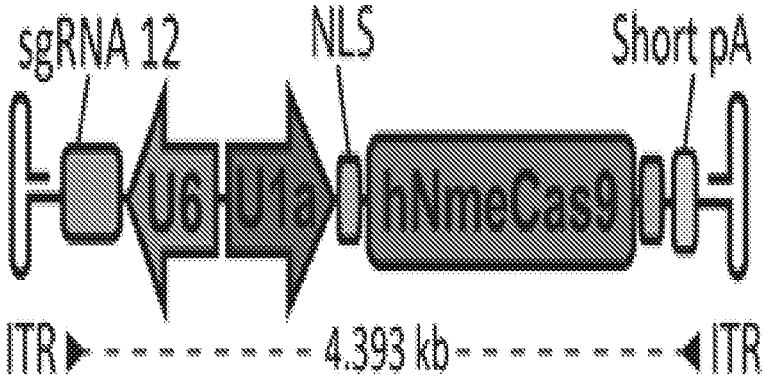
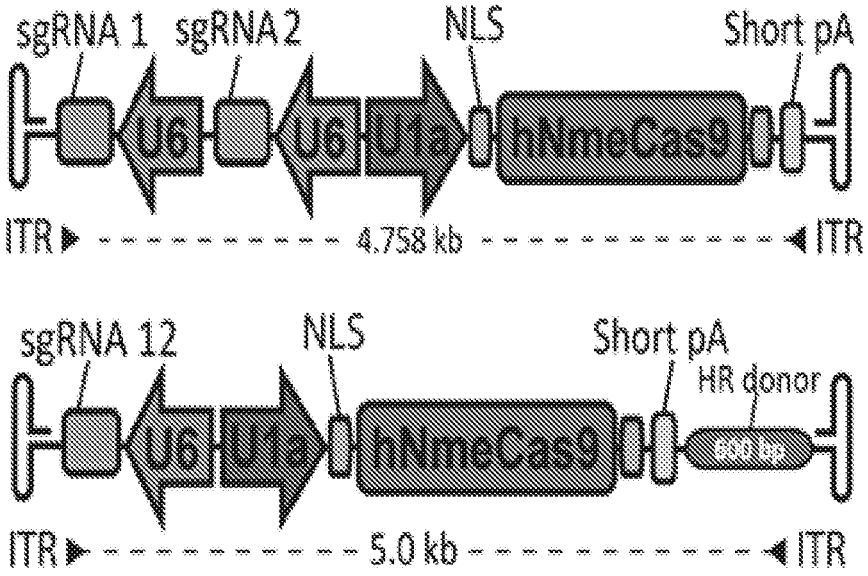


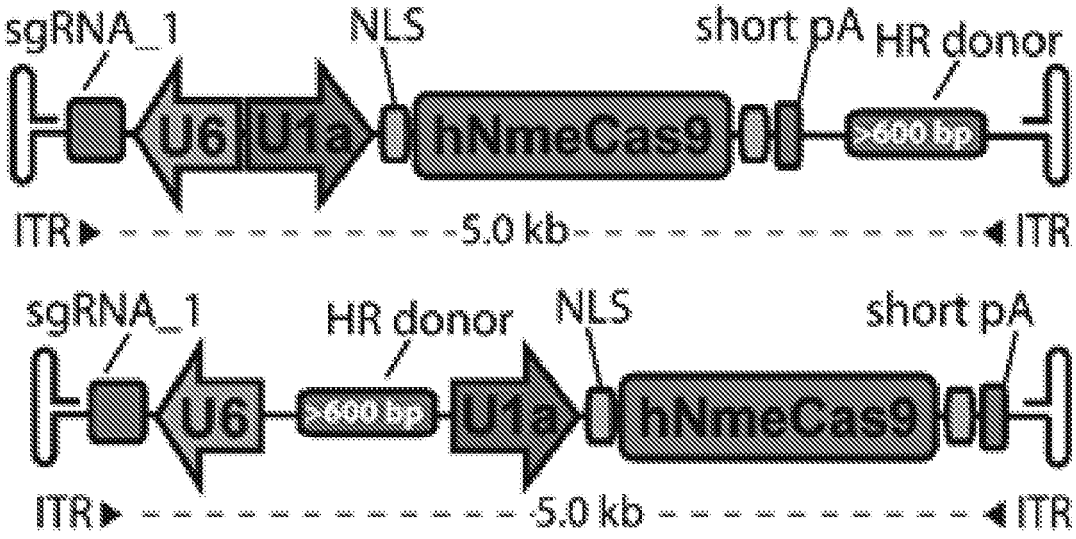
Figure 47

A



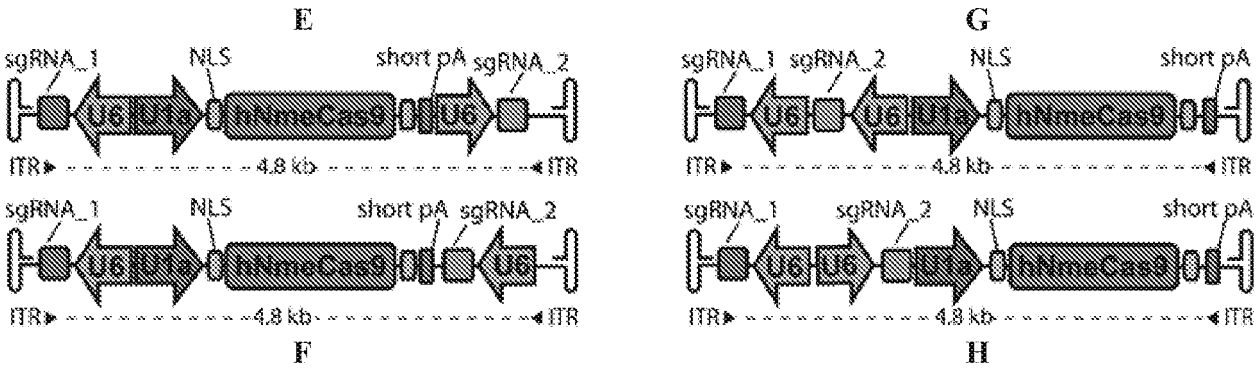
B

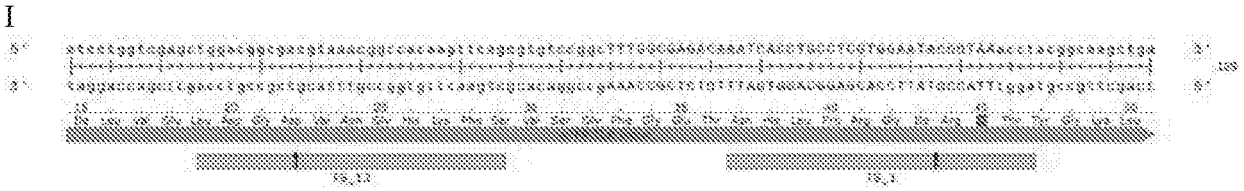
C



D

Figure 48





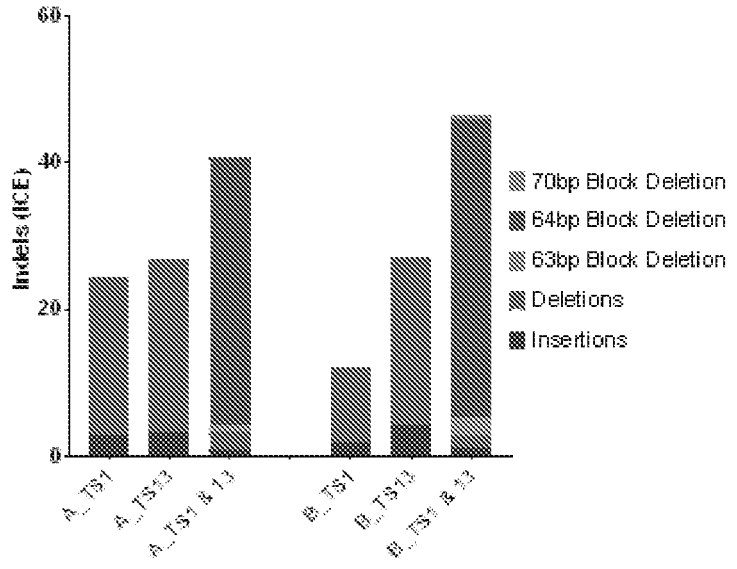


Figure 48 (cont'd)

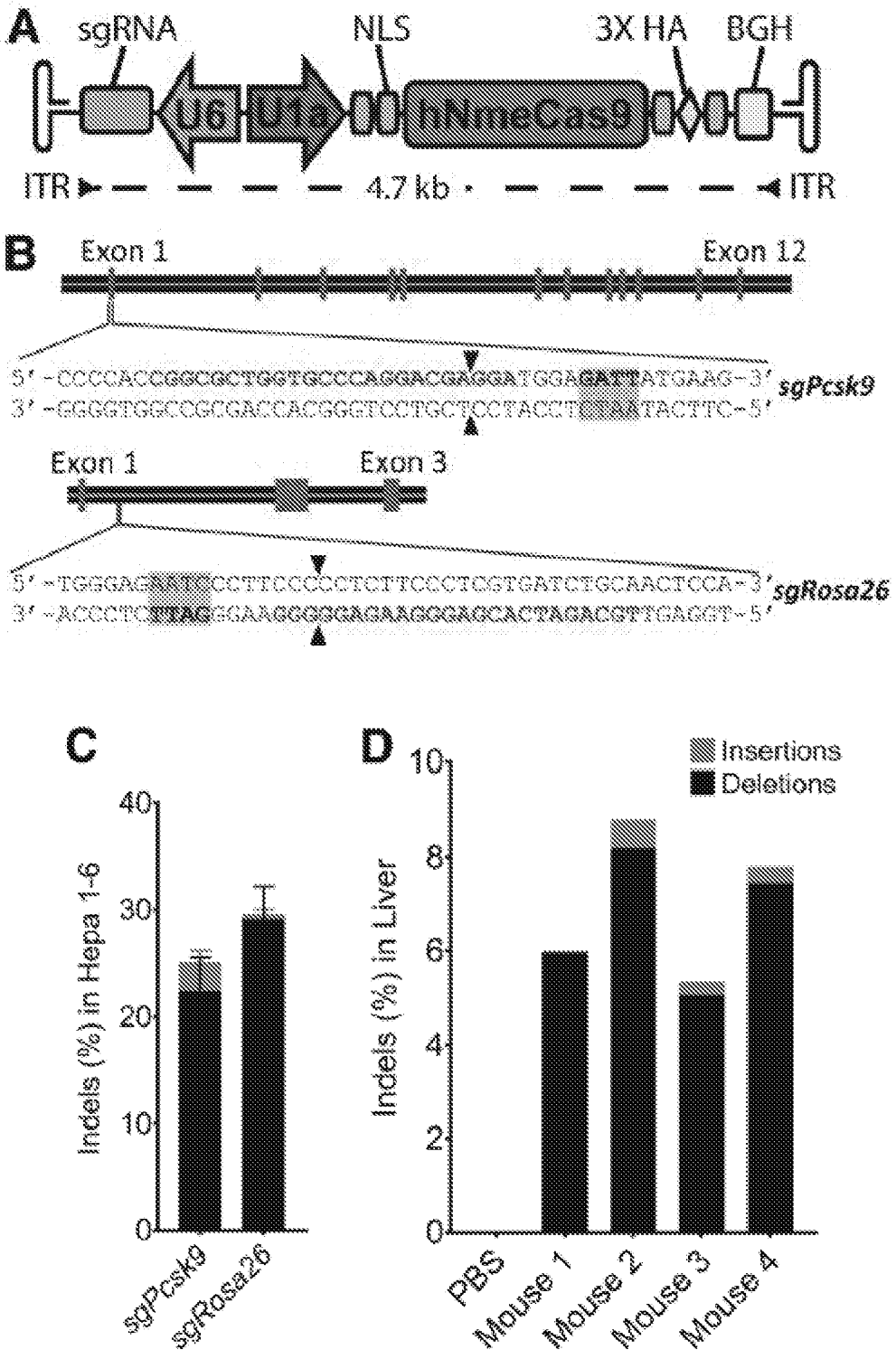

A
sgRNA
NLS
3X HA
BGH
U6
U1a
hNmeCas9
ITR
4.7 kb
ITR
B
Exon 1
Exon 12
sgPcsk9
Exon 1
Exon 3
sgRosa26
C
Indels (%) in Hepa 1-6
sgPcsk9
sgRosa26
D
Insertions
Deletions
Indels (%) in Liver
PBS
Mouse 1
Mouse 2
Mouse 3
Mouse 4

Figure 49

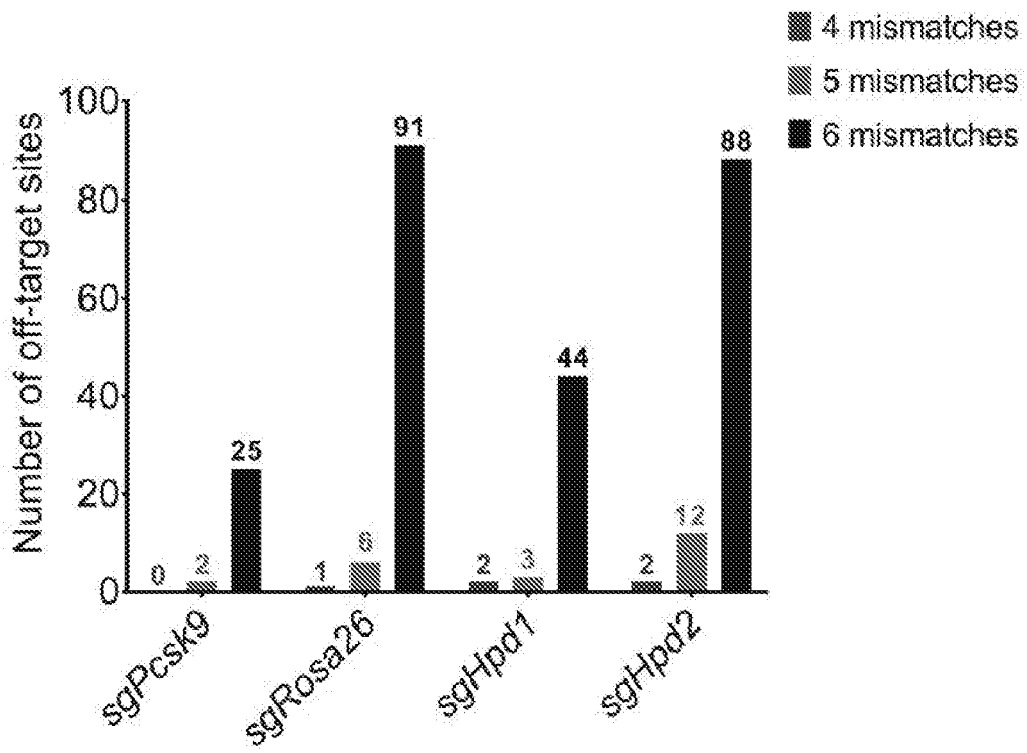

4 mismatches
5 mismatches
6 mismatches
Number of off-target sites
100
80
60
40
20
0
0
2
25
1
6
91
2
3
44
2
12
88
sgPcsk9
sgRosa26
sgHpd1
sgHpd2

Figure 50

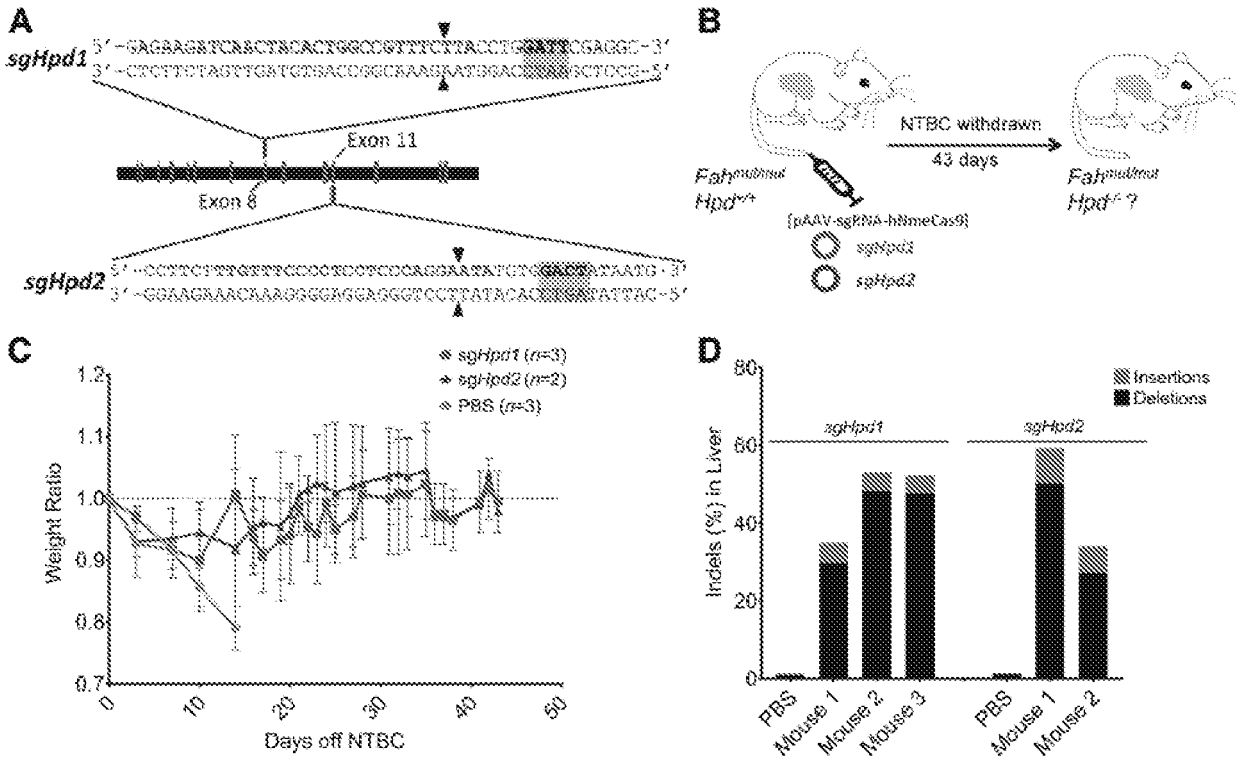

A
sgHpd1
Exon 11
Exon 8
sgHpd2
B
NTBC withdrawn
43 days
(pAAV-sgRNA-hSmeCas9)
sgHpd1
sgHpd2
C
sgHpd1 (n=3)
sgHpd2 (n=2)
PBS (n=3)
Weight Ratio
Days off NTBC
D
Insertions
Deletions
sgHpd1
sgHpd2
Indels (%) in Liver
PBS
Mouse 1
Mouse 2
Mouse 3

Figure 51

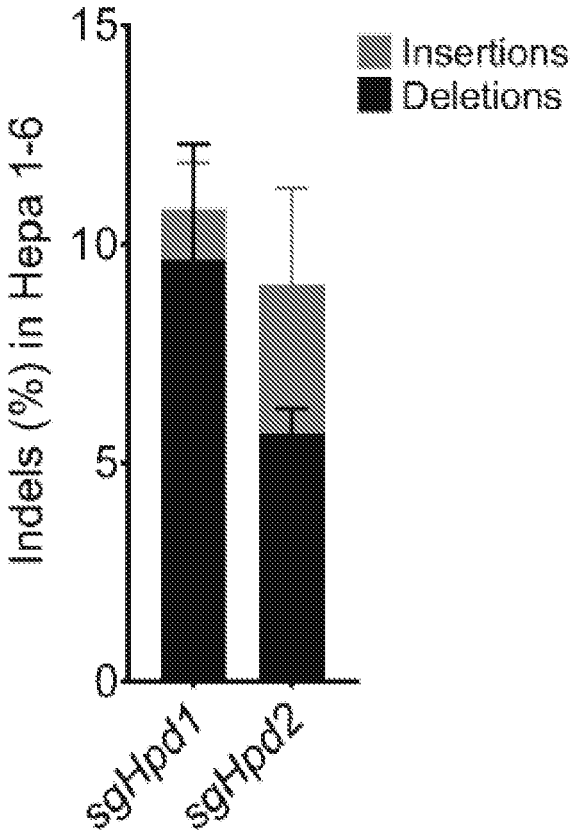

15
10
5
0
Indels (%) in Hepa 1-6
Insertions
Deletions
sgHpd1
sgHpd2

Figure 52

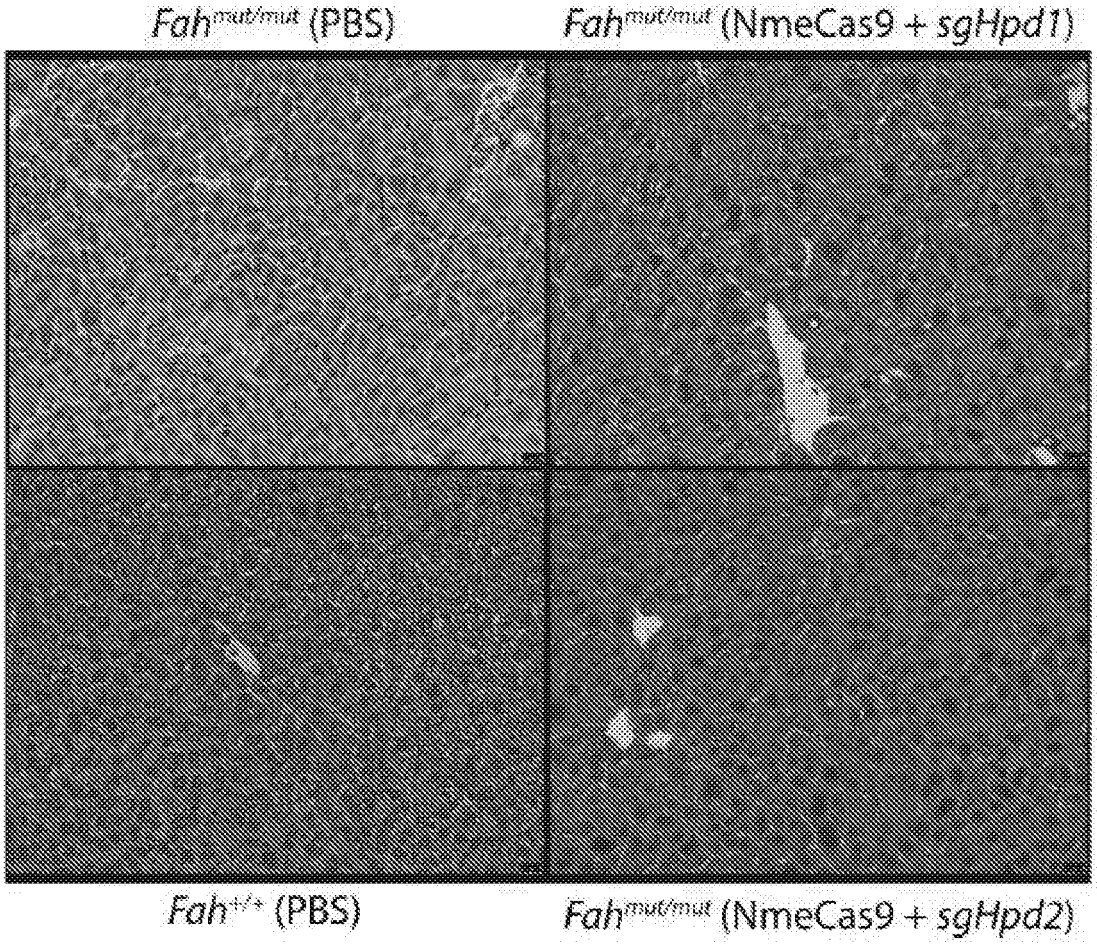

Fah^mut/mut (PBS)
Fah^mut/mut (NmeCas9 + sgHpd1)
Fah^+/+ (PBS)
Fah^mut/mut (NmeCas9 + sgHpd2)

Figure 53

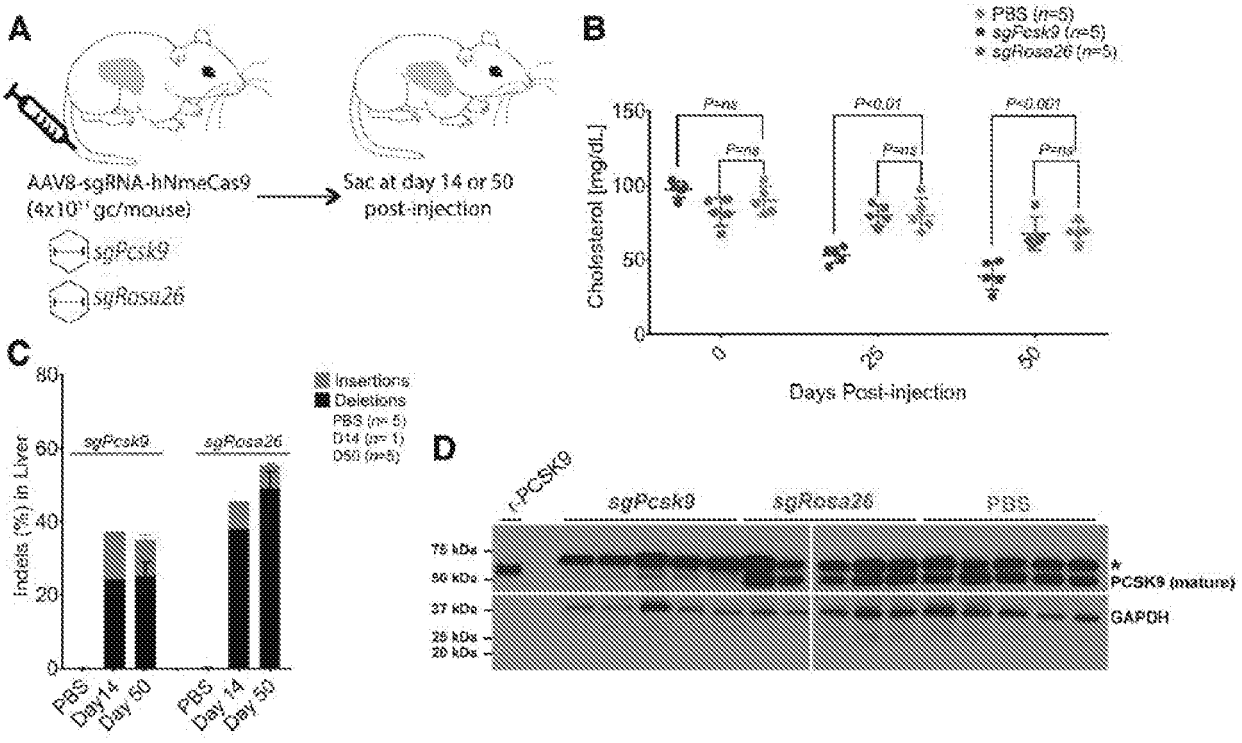
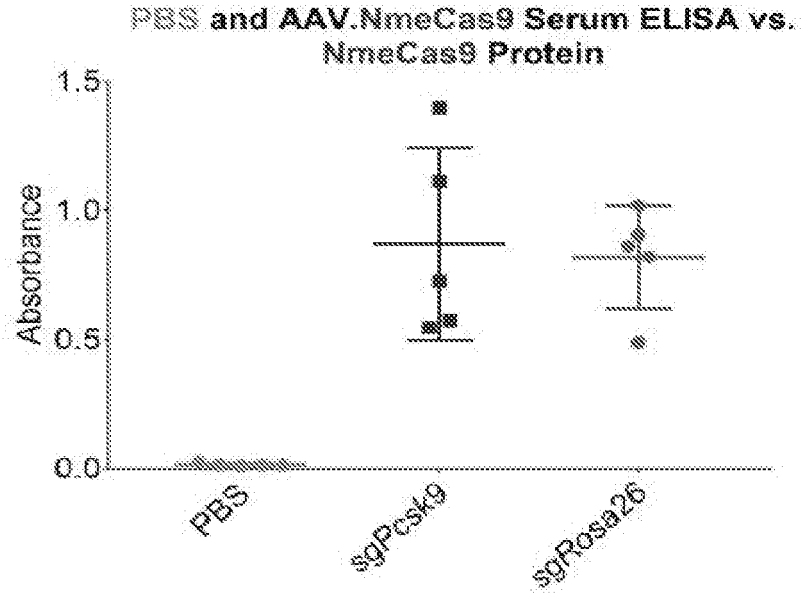

A
AAV8-sgRNA-hNmeCas9
(4x10^11 gc/mouse)
Sac at day 14 or 50
post-injection
sgPcsk9
sgRosa26
B
PBS (n=5)
sgPcsk9 (n=5)
sgRosa26 (n=5)
Cholesterol (mg/dL)
Days Post-injection
C
Insertions
Deletions
PBS (n= 5)
D14 (n= 1)
D50 (n=5)
Indels (%) in Liver
sgPcsk9
sgRosa26
PBS
Day14
Day 50
D
r.PCSK9
sgPcsk9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

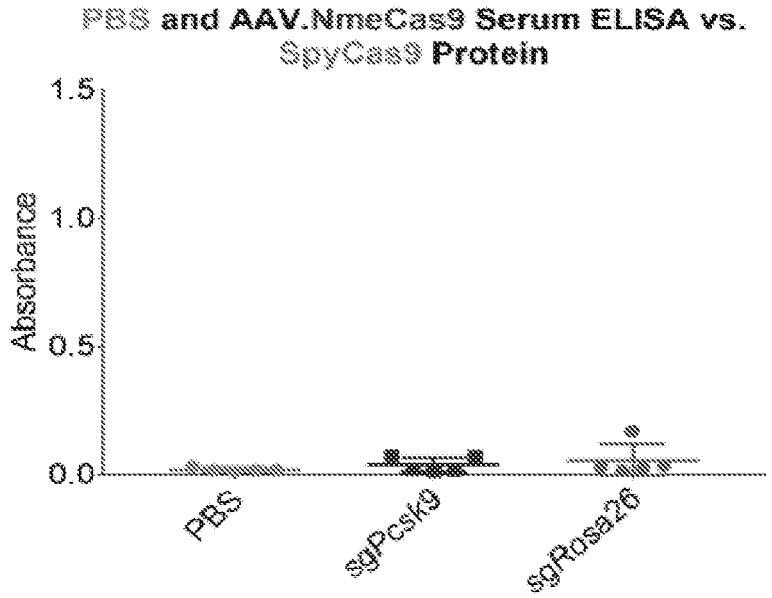

PBS and AAV.NmeCas9 Serum ELISA vs. SpyCas9 Protein
Absorbance
1.5
1.0
0.5
0.0
PBS
sgPcsk9
sgRosa26

Figure 55

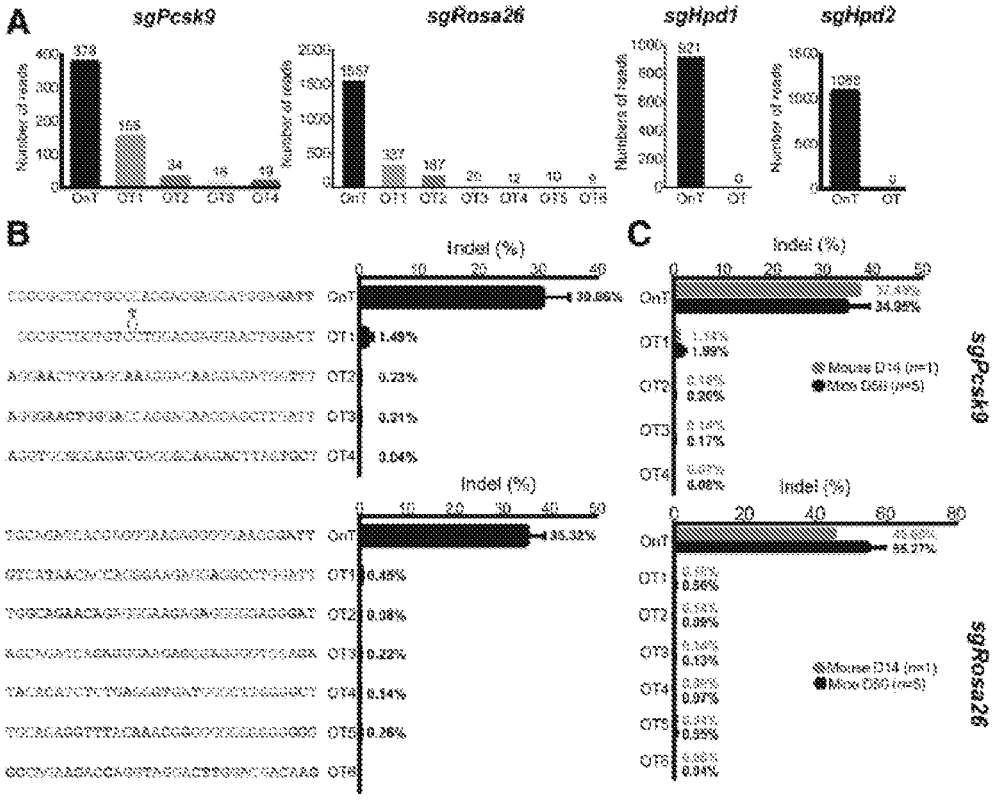
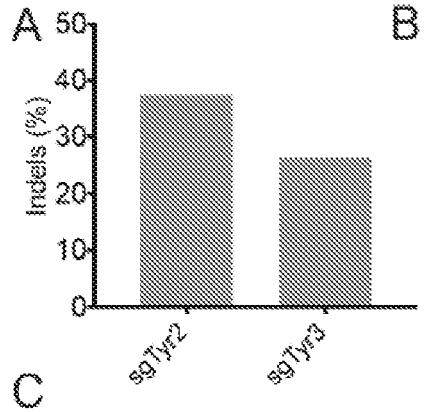

A
sgPcsk9
sgRosa26
sgHpd1
sgHpd2
Number of reads
OnT
OT1
OT2
OT3
OT4
OT5
OT6
B
C
Indel (%)
sgPcsk9
sgRosa26
Mouse D14 (n=1)
Mice D50 (n=5)

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	96	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

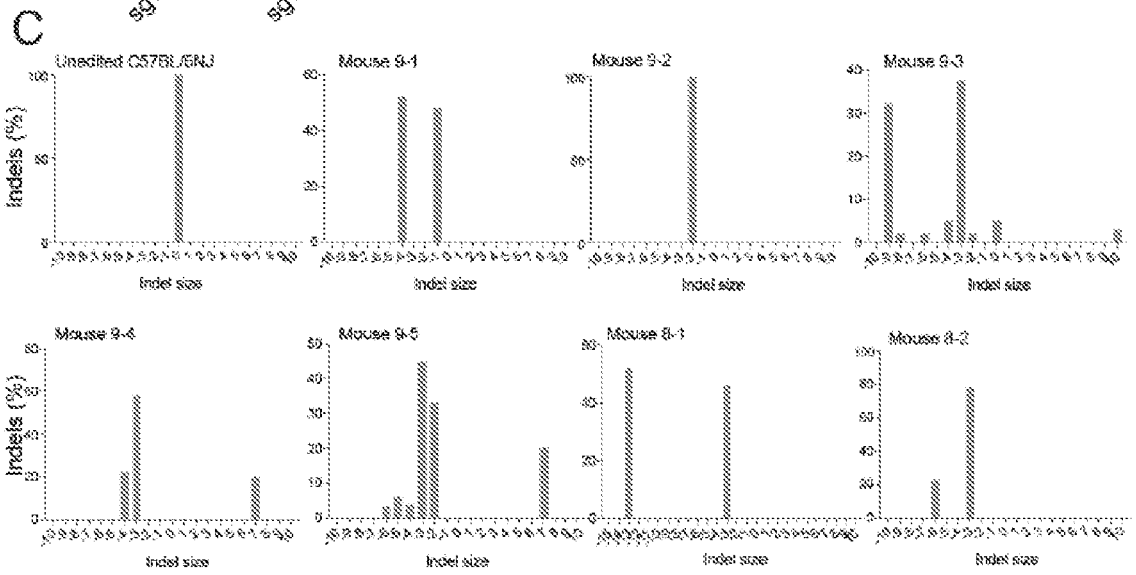
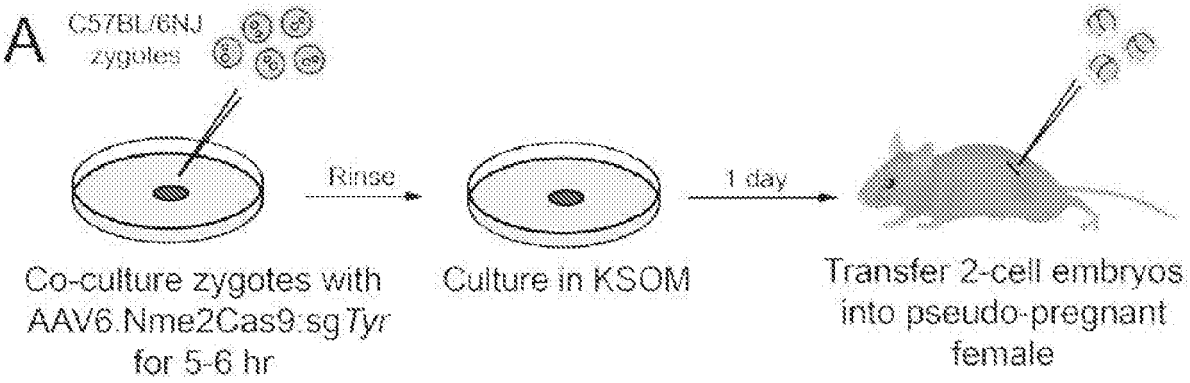
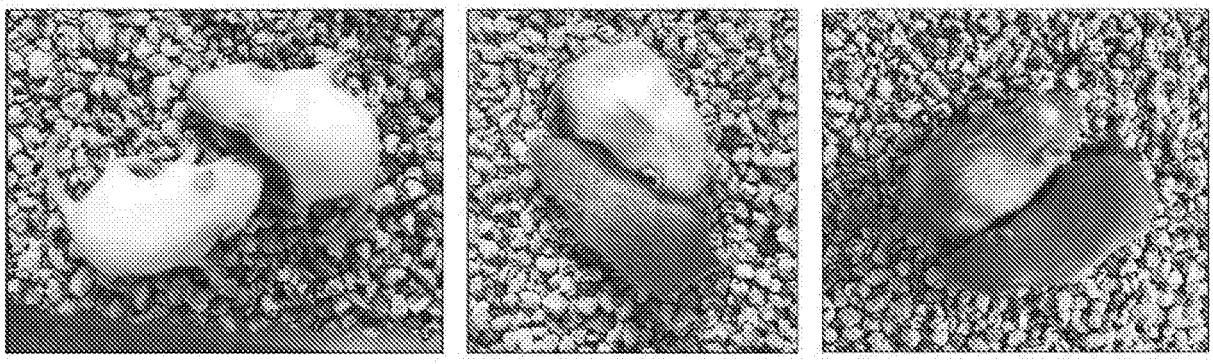


Figure 57

A



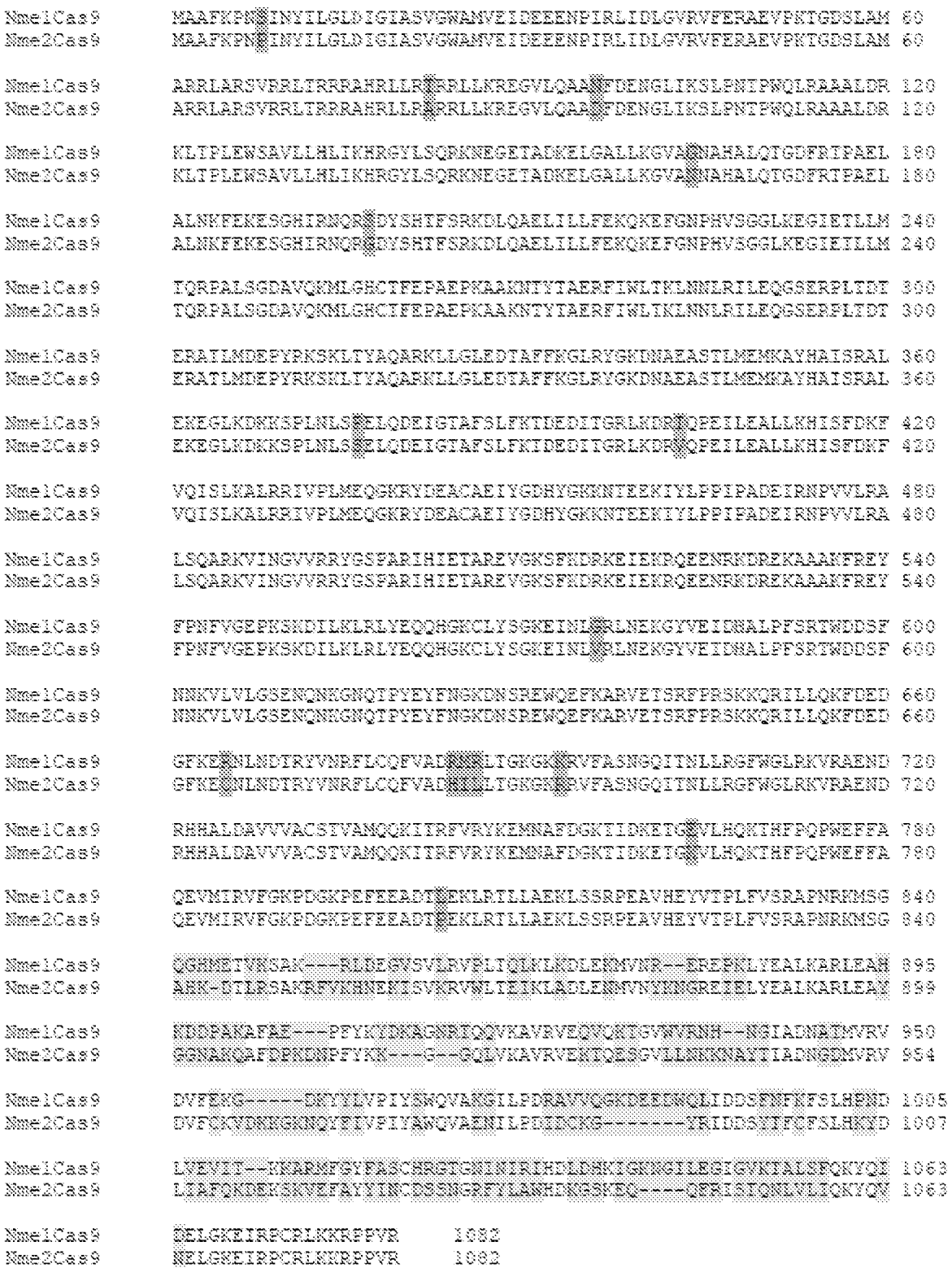
B



C

AAV Dosage	Number of embryos transferred	Number of pups recovered	Number of *Tyr*-edited pups (albino or chinchilla)	*Tyr* editing frequency (%)
3 x 10^9 GCs	50	5	5 (3)	100
3 x 10^8 GCs	28	2*	2 (1)	100

Figure 58



```
Nme1Cas9    MAAFKPNSINYILGLDIGIASVGWAMVEIDEEENPIRLIDLGVRVFERAEVPKTGDSLAM 60
Nme2Cas9    MAAFKPNPINYILGLDIGIASVGWAMVEIDEEENPIRLIDLGVRVFERAEVPKTGDSLAM 60

Nme1Cas9    ARRLARSVRRLTRRRAHRLLRTRRLLKREGVLQAANFDENGLIKSLPNTPWQLRAAALDR 120
Nme2Cas9    ARRLARSVRRLTRRRAHRLLRARRLLKREGVLQAADFDENGLIKSLPNTPWQLRAAALDR 120

Nme1Cas9    KLTPLEWSAVLLHLIKHRGYLSQRKNEGETADKELGALLKGVANAHALQTGDFRTPAEL 180
Nme2Cas9    KLTPLEWSAVLLHLIKHRGYLSQRKNEGETADKELGALLKGVANAHALQTGDFRTPAEL 180

Nme1Cas9    ALNKFEKESGHIRNQRSDYSHTFSRKDLQAELILLFEKQKEFGNPHVSGGLKEGIETLLM 240
Nme2Cas9    ALNKFEKESGHIRNQRGDYSHTFSRKDLQAELILLFEKQKEFGNPHVSGGLKEGIETLLM 240

Nme1Cas9    TQRPALSGDAVQKMLGHCTFEPAEPKAAKNTYTAERFIWLTKLNNLRILEQGSERPLTDT 300
Nme2Cas9    TQRPALSGDAVQKMLGHCTFEPAEPKAAKNTYTAERFIWLTKLNNLRILEQGSERPLTDT 300

Nme1Cas9    ERATLMDEPYRKSKLTYAQARKLLGLEDTAFFKGLRYGKDNAEASTLMEMKAYHAISRAL 360
Nme2Cas9    ERATLMDEPYRKSKLTYAQARKLLGLEDTAFFKGLRYGKDNAEASTLMEMKAYHAISRAL 360

Nme1Cas9    EKEGLKDKKSPLNLSSELQDEIGTAFSLFKTDEDITGRLKDRTQPEILEALLKHISFDKF 420
Nme2Cas9    EKEGLKDKKSPLNLSSELQDEIGTAFSLFKTDEDITGRLKDRVQPEILEALLKHISFDKF 420

Nme1Cas9    VQISLKALRRIVPLMEQGKRYDEACAEIYGDHYGKKNTEEKIYLPPIPADEIRNPVVLRA 480
Nme2Cas9    VQISLKALRRIVPLMEQGKRYDEACAEIYGDHYGKKNTEEKIYLPPIPADEIRNPVVLRA 480

Nme1Cas9    LSQARKVINGVVRRYGSPARIHIETAREVGKSFKDRKEIEKRQEENRKDREKAAAKFREY 540
Nme2Cas9    LSQARKVINGVVRRYGSPARIHIETAREVGKSFKDRKEIEKRQEENRKDREKAAAKFREY 540

Nme1Cas9    FPNFVGEPKSKDILKLRLYEQQHGKCLYSGKEINLGRLNEKGYVEIDHALPFSRTWDDSF 600
Nme2Cas9    FPNFVGEPKSKDILKLRLYEQQHGKCLYSGKEINLVRLNEKGYVEIDHALPFSRTWDDSF 600

Nme1Cas9    NNKVLVLGSENQNKGNQTPYEYFNGKDNSREWQEFKARVETSRFPRSKKQRILLQKFDED 660
Nme2Cas9    NNKVLVLGSENQNKGNQTPYEYFNGKDNSREWQEFKARVETSRFPRSKKQRILLQKFDED 660

Nme1Cas9    GFKERNLNDTRYVNRFLCQFVADRMRLTGKGKKRVFASNGQITNLLRGFWGLRKVRAEND 720
Nme2Cas9    GFKECNLNDTRYVNRFLCQFVADHILLTGKGKRRVFASNGQITNLLRGFWGLRKVRAEND 720

Nme1Cas9    RHHALDAVVVACSTVAMQQKITRFVRYKEMNAFDGKTIDKETGEVLHQKTHFPQPWEFFA 780
Nme2Cas9    RHHALDAVVVACSTVAMQQKITRFVRYKEMNAFDGKTIDKETGNVLHQKTHFPQPWEFFA 780

Nme1Cas9    QEVMIRVFGKPDGKPEFEEADTLEKLRTLLAEKLSSRPEAVHEYVTPLFVSRAPNRKMSG 840
Nme2Cas9    QEVMIRVFGKPDGKPEFEEADTPEKLRTLLAEKLSSRPEAVHEYVTPLFVSRAPNRKMSG 840

Nme1Cas9    QGHMETVKSAK---RLDEGVSVLRVPLTQLKLKDLEKMVNR--EREPKLYEALKARLEAH 895
Nme2Cas9    AHK-DTLRSAKRFVKHNEKISVKRVWLTEIKLADLENMVNYKNGREIELYEALKARLEAY 899

Nme1Cas9    KDDPAKAFAE---PFYKYDKAGNRTQQVKAVRVEQVQKTGVWVRNH--NGIADNATMVRV 950
Nme2Cas9    GGNAKQAFDPKDNPFYKK---G--GQLVKAVRVEKTQESGVLLNKKNAYTIADNGDMVRV 954

Nme1Cas9    DVFEKG-----DKYYLVPIYSWQVAKGILPDRAVVQGKDEEDWQLIDDSFNFKFSLHPND 1005
Nme2Cas9    DVFCKVDKKGKNQYFIVPIYAWQVAENILPDIDCKG-------YRIDDSYTFCFSLHKYD 1007

Nme1Cas9    LVEVIT--KKARMFGYFASCHRGTGNINIRIHDLDHKIGKNGILEGIGVKTALSFQKYQI 1063
Nme2Cas9    LIAFQKDEKSKVEFAYYINCDSSNGRFYLAWHDKGSKEQ----QFRISTQNLVLIQKYQV 1063

Nme1Cas9    DELGKEIRPCRLKKRPPVR     1082
Nme2Cas9    NELGKEIRPCRLKKRPPVR     1082
```

Figure 59



Figure 60

MAAFKPNPTNYILGLDIGIASVGWAMVEIDEEENPIRLIDLGVRVFERAEVPKTGDSLA
MARRLARSVRRLTRRRAHRLLRARRLLKREGVLQAADFDENGLIKSLPNTPWQLRA
AALDRKLTPLEWSAVLLHLIKHRGYLSQRKNEGETADKELGALLKGVANNAHALQT
GDFRTPAELALNKFEKESGHIRNQRGDYSHTFSRKDLQAELILLFEKQKEFGNPHVS
GGLKEGIETLLMTQRPALSGDAVQKMLGHCTFEPAEPKAAKNTYTAERFIWLTKLN
NLRILEQGSERPLTDTERATLMDEPYRKSKLTYAQARKLLGLEDTAFFKGLRYGKDN
AEASTLMEMKAYHAISRALEKEGLKDKKSPLNLSSELQDEIGTAFSLFKTDEDITGRL
KDRVQPEILEALLKHISFDKFVQISLKALRRIVPLMEQGKRYDEACAEIYGDHYGKKN
TEEKIYLPPIPADEIRNPVVLRALSQARKVINGVVRRYGSPARIHIETAREVGKSFKDR
KEIEKRQEENRKDREKAAAKFREYFPNFVGEPKSKDILKLRLYEQQHGKCLYSGKEI
NLVRLNEKGYVEIDHALPFSRTWDDSFNNKVLVLGSENQNKGNQTPYEYFNGKDNS
REWQEFKARVETSRFPRSKKQRILLQKFDEDGFKECNLNDTRYVNRFLCQFVADHIL
LTGKGKRRVFASNGQITNLLRGFWGLRKVRAENDRHHALDAVVVACSTVAMQQKI
TRFVRYKEMNAFDGKTIDKETGKVLHQKTHFPQPWEFFAQEVMIRVFGKPDGKPEF
EEADTPEKLRTLLAEKLSSRPEAVHEYVTPLFVSRAPNRKMSGAHKDTLRSAKRFVK
HNEKISVKRVWLTEIKLADLENMVNYKNGREIELYEALKARLEAYGGNAKQAFDPK
DNPFYKKGGQLVKAVRVEKTQESGVLLNKKNAYTIADNGDMVRVDVFCKVDKKG
KNQYFIVPIYAWQVAENILPDIDCKGYRIDDSYTFCFSLHKYDLIAFQKDEKSKVEFAY
YINCDSSNGRFYLAWHDKGSKEQQFRISTQNLVLIQKYQVNELGKEIRPCRLKKRPP
VRSYAQPKKKRKVYYYDVIDYAGYPYDVPDYAGSYPYDVPDYAGSAPAAKKKKL
DFESG*

Figure 61

MVPKKKRKVGIHGVPAAKKKRKVGIHGVPAAKKKRKMAAFKPNPINYILGLDIGIASVGWAMVEI
DEEENPIRLIDLGVRVFERAEVPKTGDSLAMARRLARSVRRLTRRRAHRLLRARRLL
KREGVLQAADFDENGLIKSLPNTPWQLRAAALDRKLTPLEWSAVLLHLIKHRGYLSQ
RKNEGETADKELGALLKGVANNAHALQTGDFRTPAELALNKFEKESGHIRNQRGDY
SHTFSRKDLQAELILLFEKQKEFGNPHVSGGLKEGIETLLMTQRPALSGDAVQKMLG
HCTFEPAEPKAAKNTYTAERFIWLTKLNNLRILEQGSERPLTDTERATLMDEPYRKS
KLTYAQARKLLGLEDTAFFKGLRYGKDNAEASTLMEMKAYHAISRALEKEGLKDKK
SPLNLSSELQDEIGTAFSLFKTDEDITGRLKDRVQPEILEALLKHISFDKFVQISLKALR
RIVPLMEQGKRYDEACAEIYGDHYGKKNTEEKIYLPPIPADEIRNPVVLRALSQARKV
INGVVRRYGSPARIHIETAREVGKSFKDRKEIEKRQEENRKDREKAAAKFREYFPNFV
GEPKSKDILKLRLYEQQHGKCLYSGKEINLVRLNEKGYVEIDHALPFSRTWDDSFNN
KVLVLGSENQNKGNQTPYEYFNGKDNSREWQEFKARVETSRFPRSKKQRILLQKFD
EDGFKECNLNDTRYVNRFLCQFVADHILLTGKGKRRVFASNGQITNLLRGFWGLRK
VRAENDRHHALDAVVVACSTVAMQQKITRFVRYKEMNAFDGKTIDKETGKVLHQ
KTHFPQPWEFFAQEVMIRVFGKPDGKPEFEEADTPEKLRTLLAEKLSSRPEAVHEYVT
PLFVSRAPNRKMSGAHKDTLRSAKRFVKHNEKISVKRVWLTEIKLADLENMVNYKN
GREIELYEALKARLEAYGGNAKQAFDPKDNPFYKKGGQLVKAVRVEKTQESGVLLN
KKNAYTIADNGDMVRVDVFCKVDKKGKNQYFIVPIYAWQVAENILPDIDCKGYRID
DSYTFCFSLHKYDLIAFQKDEKSKVEFAYYINCDSSNGRFYLAWHDKGSKEQQFRIST
QNLVLIQKYQVNELGKEIRPCRLKKRPPVRGIHGVPAAKKKRKVGIHGVPAAKKKRKVPAAKKKRKLD
AGYTYDVTDYAGSYPYDVPDYAGSPAAKKKKLD*

Figure 62

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

Figure 63

gtttaaacaaaaaaatataacgatgccccttaaagcagaagcttaaggggcagagcgttgcggcacatcttttcagacggccttattgtagcaacggttctc
attcgtttccgaaatgagaaagggagctacaacNNNNNNNNNNNNNNNNNNNNNNNNC*ggtgtttcgtcctttccacaagatata*
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Figure 64