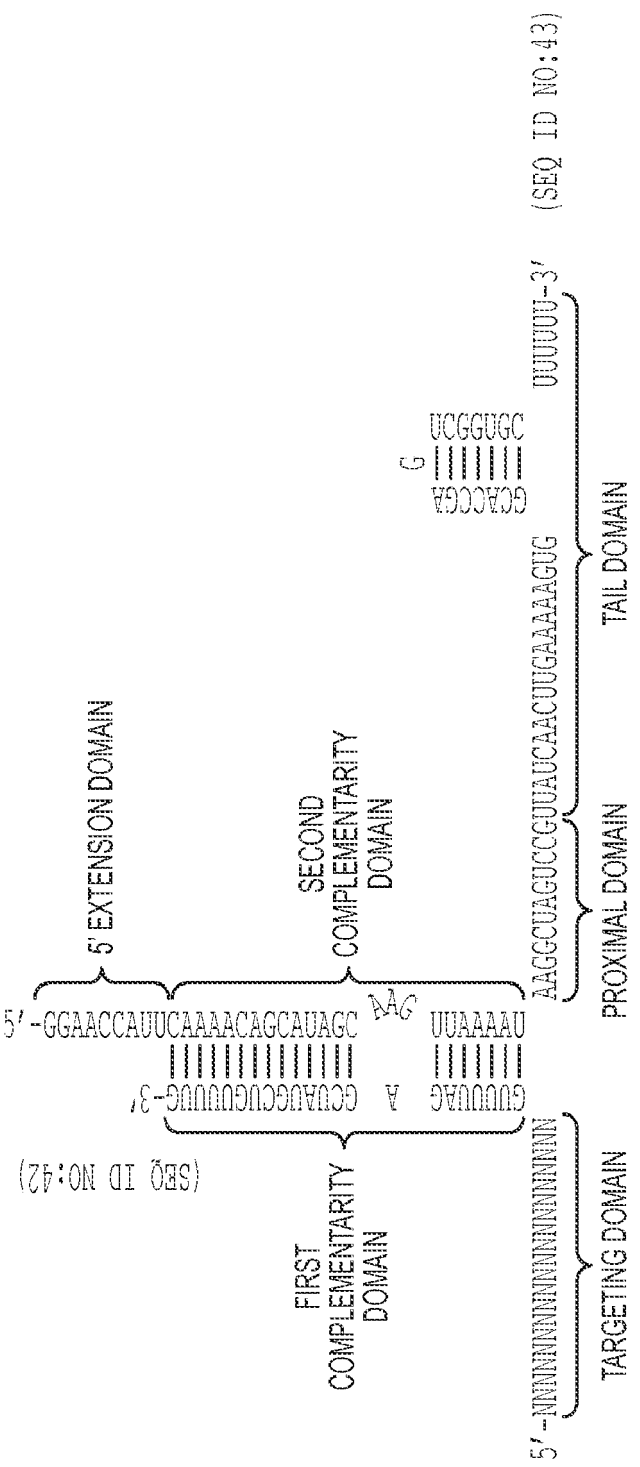

5'-GGAACCAUUCAAAACAGCAUAGC
GUUUUAG A GCUAUGCUGUUUUG-3'
(SEQ ID NO:42)
UUAAAAU
AAGGCUAGUCCGUUAUCAACUUGAAAAAGUG
UUUUUU-3'
(SEQ ID NO:43)
GCACCGA
G
UCGGUGC
5'-NNNNNNNNNNNNNNNNNNNN
5' EXTENSION DOMAIN
SECOND COMPLEMENTARITY DOMAIN
FIRST COMPLEMENTARITY DOMAIN
TARGETING DOMAIN
PROXIMAL DOMAIN
TAIL DOMAIN

FIG. 1A

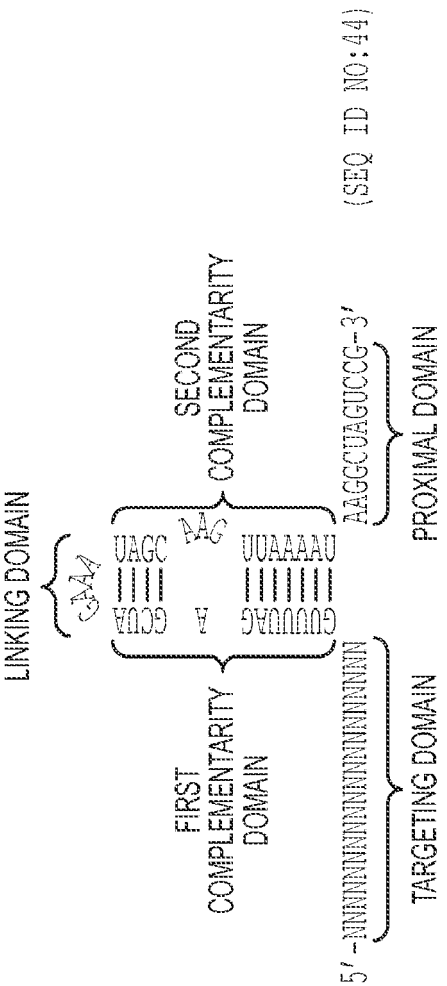

LINKING DOMAIN
GAAA
UAGC
GCUA
A
AA
UUAAAAU
GUUUAG
FIRST COMPLEMENTARITY DOMAIN
SECOND COMPLEMENTARITY DOMAIN
5'-NNNNNNNNNNNNNNNNNNNN
AAGGCUAGUCCG-3'
(SEQ ID NO:44)
TARGETING DOMAIN
PROXIMAL DOMAIN

FIG. 1B

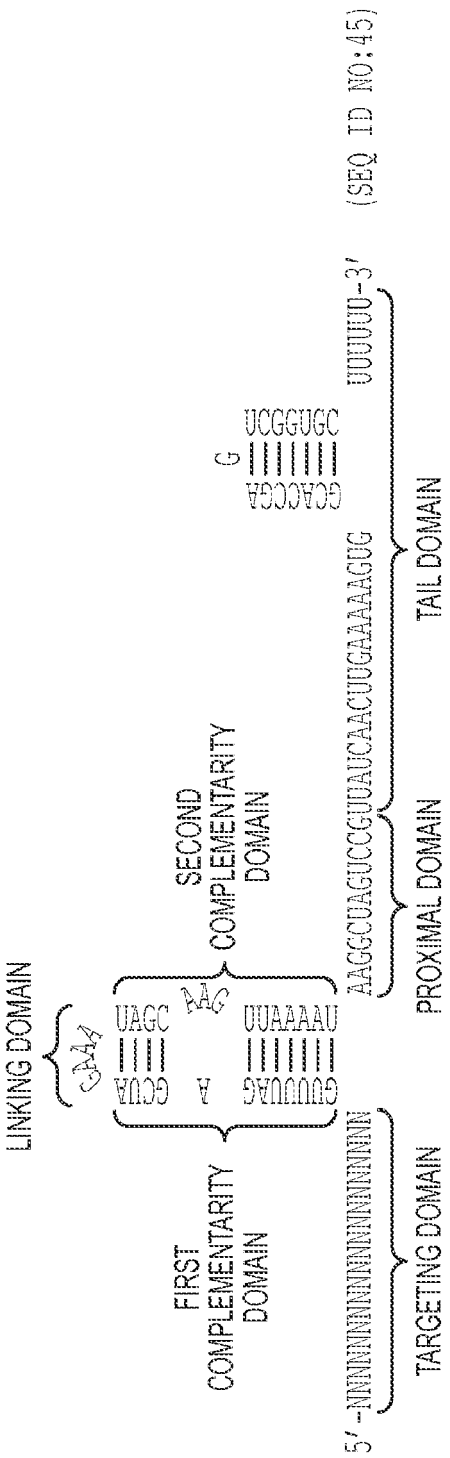

LINKING DOMAIN
CAA
UAGC
GCUA
A
GUUUAG
UUAAAAU
AAG
FIRST COMPLEMENTARITY DOMAIN
SECOND COMPLEMENTARITY DOMAIN
AAGGCUAGUCCGUUAUCAACUUGAAAAAGUG
GCACCGA
G
UCGGUGC
UUUUUU-3'
(SEQ ID NO:45)
5'-NNNNNNNNNNNNNNNNNNNN
TARGETING DOMAIN
PROXIMAL DOMAIN
TAIL DOMAIN

FIG. 1C

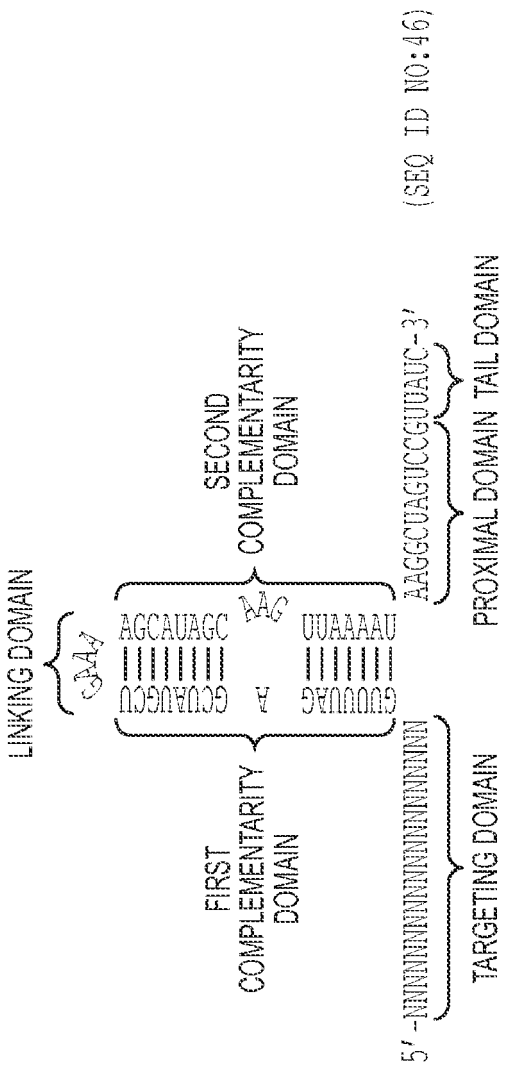

LINKING DOMAIN
SAA
AGCAUAGC
GCUAUGCU
A
AAG
UUAAAAU
GUUUAG
SECOND COMPLEMENTARITY DOMAIN
FIRST COMPLEMENTARITY DOMAIN
5'-NNNNNNNNNNNNNNNNNNNN
AAGGCUAGUCCGUUAUC-3'
(SEQ ID NO:46)
TARGETING DOMAIN
PROXIMAL DOMAIN TAIL DOMAIN

FIG. 1D

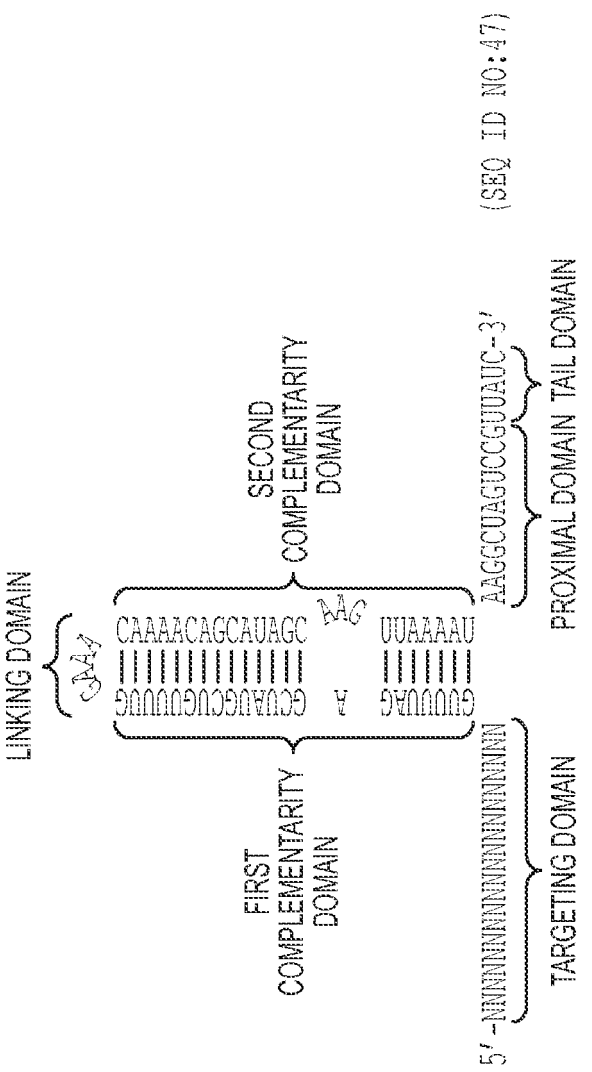

LINKING DOMAIN
SECOND COMPLEMENTARITY DOMAIN
FIRST COMPLEMENTARITY DOMAIN
5'-NNNNNNNNNNNNNNNNNNNN
TARGETING DOMAIN
PROXIMAL DOMAIN
TAIL DOMAIN
(SEQ ID NO:47)

FIG. 1E

STREPTOCOCCUS THERMOPHILUS

A) STRUCTURE (SEE, E.G., KARVELIS *ET AL.* RNA BIOLOGY. 2013; 10(5): 841-851)

FIG. 1F

ALIGNMENT

S. PYOGENES 5′-NNNNNNNNNNNNNNNNNNNNGUUUUAGAGCUAUGCUGUUUUG-3′ (SEQ ID NO:50)
S. THERMOPHILUS 5′-NNNNNNNNNNNNNNNNNNNNGUUUUAGAGCUGUGUUGUUUCG-3′ (SEQ ID NO:51)
********** ** ***** *

S. PYOGENES 5′-GAACCAUUCAAAACAGCAUAGCAAGUUAAAAUAAGGC-UAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUU-3′
S. THERMOPHILUS 5′-------GGGCGAAACAACACAGCGAGUUAAAUAAGGCUUAGUCCGUACUCAACUUGAAAAGGUGGCACCGAUUCGGUGUUUU----3′
* ***** ** *** ********** ******** ********** ********** ****

S. PYOGENES - CONT (SEQ ID NO:52)
S. THERMOPHILUS - CONT (SEQ ID NO:53)

FIG. 1G

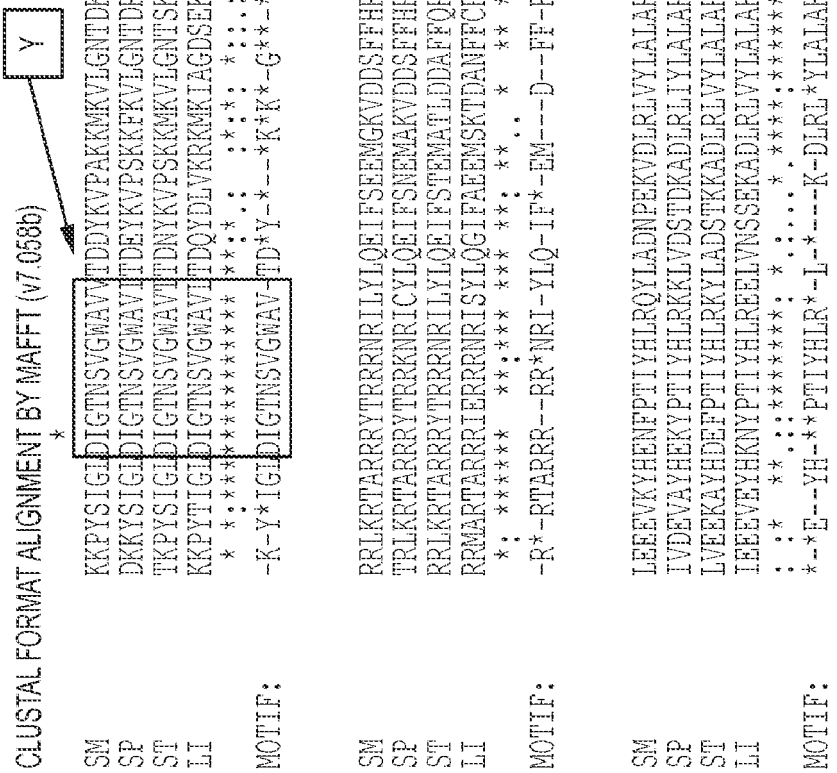

CLUSTAL FORMAT ALIGNMENT BY MAFFT (v7.058b)
Y
SM KKPYSIGLDIGTNSVGWAVITDDYKVPAKKMKVLGNTDKSHIEKNLLGALLFDSGNTAED
SP DKKYSIGLDIGTNSVGWAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDSGETAEA
ST TKPYSIGLDIGTNSVGWAVITDNYKVPSKKMKVLGNTSKKYIKKNLLGVLLFDSGITAEG
LI KKPYTIGLDIGTNSVGWAVITDQYDLVKRKMKIAGDSEKKQIKKNFWGVRLFDEGQTAAD
MOTIF: -K-Y*IGLDIGTNSVGWAV-TD*Y-*--*K*K*-G*K*-*--I*KN*-G--LFD-G-TA--
SM RRLKRTARRYTRRRNRILYLQEIFSEEMGKVDDSFFHRLEDSFLVTEDKRGERHPIFGN
SP TRLKRTARRYTRRKNRICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHPIFGN
ST RRLKRTARRYTRRRNRILYLQEIFSTEMATLDDAFFQRLDDSFLVPDDKRDSKYPIFGN
LI RRMARTARRRIERRRNRISYLQGIFAEEMSKTDANFFCRLSDSFYVDNEKRNSRHPFFAT
MOTIF: -R*-RTARR--RR*NRI-YLQ-IF*-EM---D--FF-RL-*SF-V-**K*--**P*F--
SM LEEEVKYHENFPTIYHLRQYLADNPEKVDLRLVYLALAHIIKFRGHFLIEGKFDTRNNDV
SP IVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYLALAHMIKFRGHFLIEGDLNPDNSDV
ST LVEEKAYHDEFPTIYHLRKYLADSTKKADLRLVYLALAHMIKYRGHFLIEGEFNSKNNDI
LI IEEEVEYHKNYPTIYHLREELVNSSEKADLRLVYLALAHIIKYRGNFLIEGALDTQNTSV
MOTIF: *-*E--YH-**PTIYHLR*-L-*---K-DLRL*YLALAH*IK*RGNFLIEG-**--N--*

FIG. 2A

```
SM      QRLFQEFLAVYDNTENSS------LQEQNVQVEEILTDKISKSAKKDRVLKLFPNEKSN
SP      DKLFIQLVQTYNQLEENP------INASGVDAKAILSARLSKSRRLENLIAQLPGEKKN
ST      QKNFQDFLDTYNAIFESDL------SLENSKQLEEIVKDKISKLEKKDRILKLFPGEKNS
LI      DGIYKQFIQTYNQVFASGIEDGSLKKLEDNKDVAKILVEKVTRKEKLERILKLYPGEKSA
        .  : ::: .:  *   *          ..  :   *:  :::::  : :::    * **.
MOTIF:  *__*_***__Y*__f_____________________*____I*__****__*_*_**_____P-EK__

SM      GRFAEFLKLIVGNQADFKKHFELEEKAPLQFSKDTYEELEVLLAQIGDNYAELFLSAKK
SP      GLFGNLIALSLGITPNFKSNFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLAAKN
ST      GIFSEFLKLIVGNQADFRKCFNLDEKASLHFSKESYDEDLETLLGYIGDDYSDVFLKAKK
LI      GMTAQFISLIVGSKCNFQKPFDLIEKSDIECAKDSYEEDLESLLALIGDEYAELFVAAKN
        * *.::::  * :*    .*:.  *:* * .: .: .*:.:*:::*:. **  .***:*:::*: **:
MOTIF:  G-F-***_L-*G___*F*__F*L-E-*_*__*K**Y***L*-LL__IGD*Y***F*-AK*

SM      LYDSILLSGILTVTDVGTKAPLSASMIQRYNEHQMDLAQLKQFIRQKLSDKYNEVFSDVS
SP      LSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDLTLLKALVRQQLPEKYKEIFFDQS
ST      LYDAILLSGFLTVTDNETEAPLSSAMIKRYNEHKEDLALLKEYIRNISLKTYNEVFKDDT
LI      AYSAVVLSSITTVAETETNAKLSASMIERFDTHEEDLGELKAFIKLHLPKHYEEIFSNTE
          .:::** ::: *     *:* **;:**:*:: *  **  **   ::       .  *:*:* :
MOTIF:  __***LS-**-V____T*A-LS**MI*R**-H--DL--LK--**_____Y*E*F-*__

SM      KDGYAGYIDGKTNQEAFYKYLKGLLNKIEGSGYFLDKIEREDFLRKQRTFDNGSIPHQIH
SP      KNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIPHQIH
ST      KNGYAGYIDGKTNQEDFYVYLKKLLAEFEGADYFLEKIDREDFLRKQRTFDNGSIPYQIH
LI      KHGYAGYIDGKTKQADFYKYMKMTLENIEGADYFIAKIEKENFLRKQRTFDNGAIPHQLH
        * *********  :.*  **  :*:*  *  :::*:.  ::  *:::*:.:**********:**:*
MOTIF:  K-GYAGYIDG-*-Q--FY-***K--L-***G*__**-K****E**LRKQRTFDNG*IP*Q*H
```

FIG. 2B

```
SM      LQEMRAIIRQAEFYPFLADNQDRIEKLLTTRIPYYVGPLARGKSDFAWLSRKSADKITP
SP      LGELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETITP
ST      LQEMRAILDKQAKFYPFLAKNKERIEKILTFRIPYYVGPLARGNSDFAWSIRKRNEKITP
LI      LEELEAILHQQAKYYPFLKENYDKIKSLVTFRIPYFVGPLANGQSEFAWLTRKADGEIRP
        * *: **: :*  :*****  * .:*:. .:*****:*****.*:* ***  **    * *
MOTIF:  L-E*-AI*-*Q--*YPFL--N-**I*-**TRIPY*VGPLA-G*S-FAW--RK----I-P

SM      WNFDEIVDKESSAEAFTNRMTNYDLYLPNQKVLPKHSLLYEKFTVYNELTKVKYTE-QG
SP      WNFEEVVDKGASQSFTERMTNFDKNLPNEKVLPKHSLIYEYFTVYNELTKVKYVTEGMR
ST      WNFEDVIDKESSAEAFTNRMTSFDLYLPEEKVLPKHSLIYETFNVYNELTKVRFIAESMR
LI      WNIEEKVDFGKSAVDFTEKMTNKDTYLPKENVLPKHSLCYQKYLVYNELTKVRYIND-QG
        **:::: :*   **  ***:**  *  **:::*******  :: : ********:: :
MOTIF:  WN***-*D---SA--FI**MT--D--LP***VLPKHSL-Y*-*-VVNELTKV**---*---

SM      KTAFFDANMKQEIFDGVFKVYRKVTKDKLMDFLEKEFDEFRIVDLTGLDKENKVFNASYG
SP      KPAFLSGEQKKAIVDLLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDR---FNASLG
ST      DVQFLDSKQKKDIVRLYFKDKRKVTDKDIIEYL-HAIYGVDGIELKGIEKQ---FNSSLS
LI      KTSYFSGQEKEQIFNDLFKQKRKVKKKDLELFL-RNMSHVESPTIEGLEDS---FNSSYS
          :::::: *: *.  **  ***. ,::  : :.     : *:::      **:* .
MOTIF:  ---**---*-K*-I----FK--RKV-----*-----*-*-------*-G**------FN*S--

SM      TYHDLCKIL-DKDFLDNSKNEKILEDIVLTLTLFEDREMIRKRLENYSDLLTKEQVKKLE
SP      TYHDLLKIIKDKDFLDNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLFDDKVMKQLK
ST      TYHDLLNIINDKEFLDDSSNEAIIEEIIHTLTIFEDREMIKQRLSKFENIFDKSVLKKLS
LI      TYHDLLKVGIKQEILDNPVNTEMLENIVKILTVFEDKRMIKEQLQQFSDVLDGVVLKKLE
        ***** ::   :::***:  * :**:**:  ***:****: ** ***:* : ::  :*:* .
MOTIF:  TYHDL-**----***LD*--N--**E*I*--LT*FED*-MI-**L--*--**-----*K*L-
```

FIG. 2C

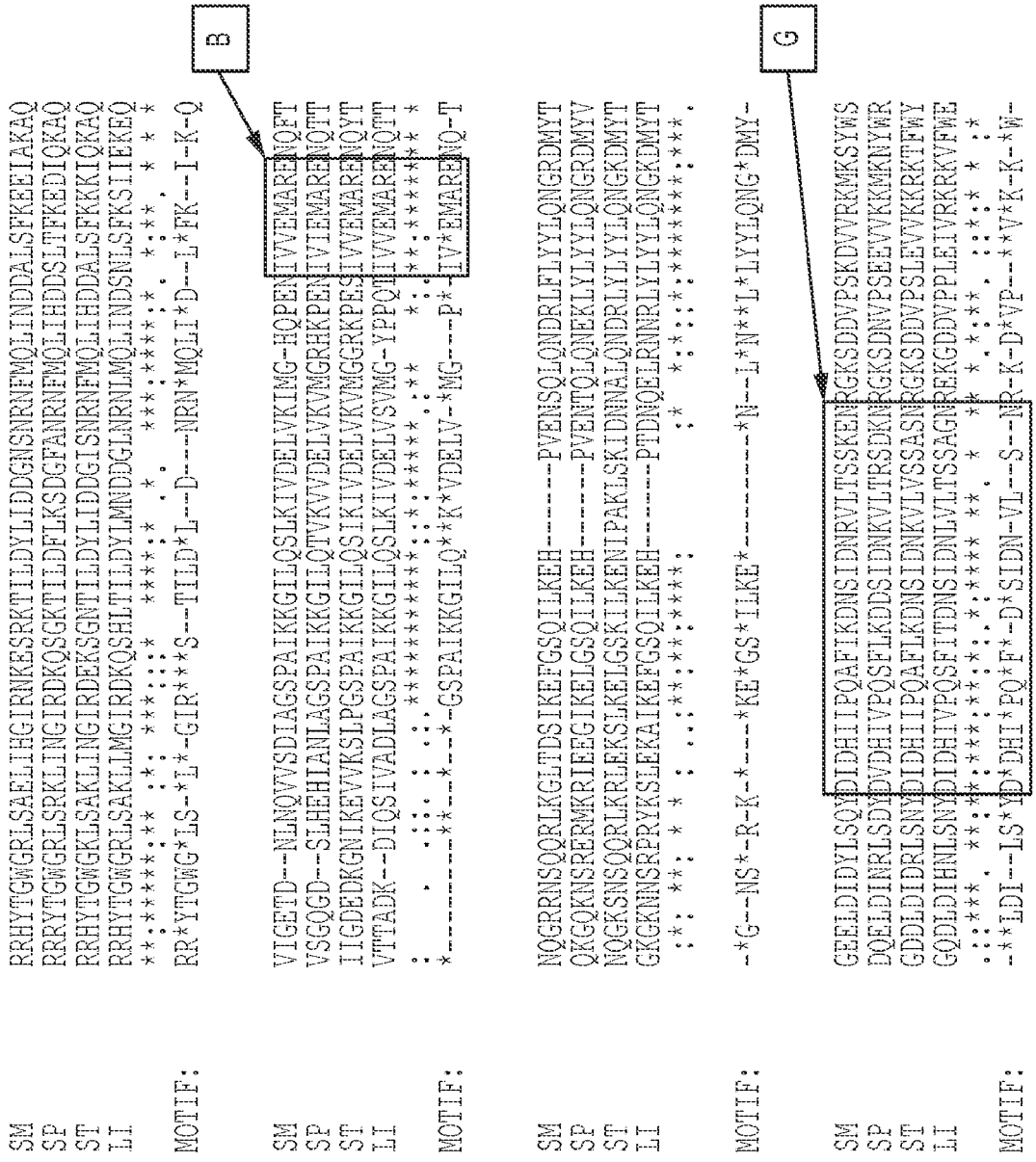


FIG. 2D



FIG. 2E

```
SM       GNSDK-LIPRKTKKFYWDTKKYGGFDSPTVAYSILVIADIEKGKSKKLKTVKALVGVTIM
SP       RNSDK-LIARKKD----WDPKKYGGFDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIM
ST       PNSNENLVGAKEY----LDPKKYGGYAGISNSFTVLVKGTIEKGAKKKITNVLEFQGISIL
LI       GNSSK-LIPRKTN----WDPMKYGGLDSPNMAYAVVI--EYAKGKN-KLVFEKKIIRVTIM
                  *  *    *  ****  .  :::::::      **  .  **    :  ::**:
         MOTIF:   -NS--*-I*--K-------D--KYGG-------*******-------KG----K*-------*--**I*

SM       EKMTFERDPVAFLERKGYRNVQEENIIKLPKYSLFKLENGRKRLIAS-------------ARELQK
SP       ERSSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRKRMLAS-------------AGELQK
ST       DRINYRKDKLNFLLEKGYKDI--ELIIELPKYSLFELSDGSRRMLASILSTNNKRGEIHK
LI       ERKAFEKDEKAFLEEQGYRQP--KVLAKLPKYTLYECEEGRRRMLAS-------------ANEAQK
         ::  :***:    **   :**:*:    . :.*****:***: .:* .:*.***          * .*
         **--*-**----FL--*GY**------*-*LPKY*I**--*G-*R*LAS-------------E-*K

SM       GNEIVLPNHLGTLIYHAKNIHKV------DEPKHLDYVDKHKDEFKELLDVVSNFSKKYT
SP       GNELALPSKYVNFIYLASHYEKLKGSPEDNEQKQL-FVEQHKHYLDEIIEQISEFSKRVI
ST       GNQIFLSQKFVKLIYHAKRISNT-------INENHRKYVENHKKEFEELFYYILEFNENYV
LI       GNQQVLPNHLVTLLHHAANCEVS-------DGKSLDYIESNREMFAELLAHVSEFAKRYT
         **:  * .:  .:*: * .            : :  :::::::. : *:::  : :* : :
         GN*--L--*---*I*-A----------------*-*---***-**--*-E**--*-*F-*---

SM       LAEGNLEKIKELYAQNNGEDLKELASSFI--------NLLTFTAIGAPATFKFFDKNIDR
SP       LADANLDKVLSAYNKHRDKPIREQAENII--------HLFTLTNLGAPAAFKYFDTTIDR
ST       GAKKNGKLLNSAFQSWQNHSIDELCSSFIGPTGSERKGLFELTSRGSAADFEFLGVKIPR
LI       LAEANLNKINQLFEQNKEGDIKAIAQSFV--------DLMAFNAMGAPASFKFFETTIER
           *  *  . : . : . :  .  :  .:::::      *: ::  *: * *::::  . * *
         -A--N---*---*-------*--------**---------L*-*---G*-A-F***---I-R
```

FIG. 2F

```
SM      KR-YTSTTEILNATLIHQSITGLYETRIDLNKLGGD  (SEQ ID NO:1)
SP      KR-YTSTKEVLDATLIHQSITGLYETRIDLSQLGGD  (SEQ ID NO:2)
ST      YRDYTPSSLLKDATLIHQSVTGLYETRIDLAKLGEG  (SEQ ID NO:3)
LI      KR-YNNLKELLNSTIIYQSITGLYESRKRLD----D  (SEQ ID NO:4)
          * *.  . : :::*:**:***** *   .
Motif;  -R-Y------*-**T*I*QS*TGLYE*R--L-------
```

FIG. 2G

ALIGNMENT OF THE N TERMINAL RJNCV-LIKE DOMAINS DISCLOSED IN CHYLINSKI *ET AL.* (EXCLUDING SEQUENCE OUTLIERS).
(CLUSTAL FORMAT ALIGNMENT BY MAFFT (V7.058B))

1	DIGTNSVGWAVT	(SEQ ID NO:54)	39	DLGVGSIGFAIV	(SEQ ID NO:81)
12	DIGTNSVGWAVT	(SEQ ID NO:55)	34	DIGYASIGWAVI	(SEQ ID NO:82)
3	DVGTNSVGWAVT	(SEQ ID NO:56)	47	DTGTNSLGWAIV	(SEQ ID NO:83)
20	DVGTNSVGWAVT	(SEQ ID NO:57)	50	DLGTNSIGWCLL	(SEQ ID NO:84)
15	DMGTNSVGWAVT	(SEQ ID NO:58)	49	DIGTDSLGWAVF	(SEQ ID NO:85)
4	DVGTSSVGWAVT	(SEQ ID NO:59)	18	DIGSNSIGFAVV	(SEQ ID NO:86)
7	DIGTASVGWAVT	(SEQ ID NO:60)	41	DLGVGSIGVAVA	(SEQ ID NO:87)
6	DVGTGSVGWAVT	(SEQ ID NO:61)	45	DLGIASCGWGVV	(SEQ ID NO:88)
9	DIGTNSVGWAVV	(SEQ ID NO:62)			
10	DIGTNSVGWAVI	(SEQ ID NO:63)			
11	DIGTNSVGWAVL	(SEQ ID NO:64)			
42	DLGTNSIGWAVV	(SEQ ID NO:65)			
48	DLGTNSIGWAI-	(SEQ ID NO:66)			
43	DLGTNSIGWAIV	(SEQ ID NO:67)			
2	DIGTNSVGWCVT	(SEQ ID NO:68)			
14	DIGTNSVGYAVT	(SEQ ID NO:69)			
5	DMGTGSIGWAVT	(SEQ ID NO:70)			
16	DIGTSSVGWAAI	(SEQ ID NO:71)			
8	DLGTGSVGWAVV	(SEQ ID NO:72)			
22	DLGVGSVGWAIV	(SEQ ID NO:73)			
23	DLGIASIGWAII	(SEQ ID NO:74)			
24	DLGIASVGWAIV	(SEQ ID NO:75)			
25	DLGVASVGWSIV	(SEQ ID NO:76)			
26	DIGIASVGWAIL	(SEQ ID NO:77)			
28	DLGISSVGWSVI	(SEQ ID NO:78)			
32	DIGIASVGWSVI	(SEQ ID NO:79)			
33	DVGIGSIGWAVI	(SEQ ID NO:80)			

FIG. 3A

21	DLGIASVGWCLT	(SEQ ID NO:89)
27	DIGIGSVGVGIL	(SEQ ID NO:90)
29	DIGITSVGYGLI	(SEQ ID NO:91)
30	DIGITSVGFGII	(SEQ ID NO:92)
31	DVGITSTGYAVL	(SEQ ID NO:93)
40	DLGITSFGYAIL	(SEQ ID NO:94)
17	DIGNASVGWSAF	(SEQ ID NO:95)
19	DVGTNSCGWVAM	(SEQ ID NO:96)
35	DVGERSIGLAAV	(SEQ ID NO:97)
36	DVGLNSVGLAAV	(SEQ ID NO:98)
37	DVGLMSVGLAAI	(SEQ ID NO:99)
38	DVGTFSVGLAAI	(SEQ ID NO:100)
13	DIGTGSVGYACM	(SEQ ID NO:101)
44	DLGTTSIGFAHI	(SEQ ID NO:102)
46	DLGTNSIGSSVR	(SEQ ID NO:103)
	* * * *	

FIG. 3B

ALIGNMENT OF THE N TERMINAL RuCV-LIKE DOMAINS DISCLOSED IN CHYLINSKI *ET AL.*
(CLUSTAL FORMAT ALIGNMENT BY MAFFT (v7.058b))

1	D----IGTNSVGWAVT	(SEQ ID NO:104)	59	D----IGIASIGWAVI	(SEQ ID NO:131)
12	D----IGTNSVGWAVT	(SEQ ID NO:105)	61	D----IGIASVGWAII	(SEQ ID NO:132)
3	D----VGTNSVGWAVT	(SEQ ID NO:106)	64	D----VGIASVGWAVI	(SEQ ID NO:133)
20	D----VGTNSVGWAVT	(SEQ ID NO:107)	62	D----IGIASVGWAL-	(SEQ ID NO:134)
15	D----MGTNSVGWAVT	(SEQ ID NO:108)	67	D----IGIASVGWAMV	(SEQ ID NO:135)
4	D----VGTSSVGWAVT	(SEQ ID NO:109)	32	D----IGIASVGWSVI	(SEQ ID NO:136)
7	D----IGTASVGWAVT	(SEQ ID NO:110)	28	D----LGISSVGWSVI	(SEQ ID NO:137)
6	D----VGTGSVGWAVT	(SEQ ID NO:111)	63	D----IGITSVGWAVI	(SEQ ID NO:138)
9	D----IGTNSVGWAVV	(SEQ ID NO:112)			
10	D----IGTNSVGWAVI	(SEQ ID NO:113)			
52	D----IGTNSIGWAVI	(SEQ ID NO:114)			
11	D----IGTNSVGWAVL	(SEQ ID NO:115)			
42	D----LGTNSIGWAVV	(SEQ ID NO:116)			
48	D----LGTNSIGWAI-	(SEQ ID NO:117)			
43	D----LGTNSIGWALV	(SEQ ID NO:118)			
2	D----IGTNSVGWCVT	(SEQ ID NO:119)			
14	D----IGTNSVGYAVT	(SEQ ID NO:120)			
5	D----MGTGSIGWAVT	(SEQ ID NO:121)			
16	D----IGTSSVGWAAI	(SEQ ID NO:122)			
8	D----LGTGSVGWAVV	(SEQ ID NO:123)			
22	D----LGVGSVGWAIV	(SEQ ID NO:124)			
23	D----LGIASIGWAII	(SEQ ID NO:125)			
24	D----LGIASVGWAIV	(SEQ ID NO:126)			
68	D----LGIASVGWAVV	(SEQ ID NO:127)			
25	D----LGVASVGWSIV	(SEQ ID NO:128)			
26	D----IGIASVGWAIL	(SEQ ID NO:129)			
66	D----IGIASVGWAVL	(SEQ ID NO:130)			

FIG. 4A

```
33 D---VGIGSIGWAVI (SEQ ID NO:139) 36 D---VGLNSVGLAAV (SEQ ID NO:166)
57 D---LGISSLGWAIV (SEQ ID NO:140) 37 D---VGIMSVGLAAI (SEQ ID NO:167)
39 D---LGVGSIGFAIV (SEQ ID NO:141) 38 D---VGTFSVGLAAI (SEQ ID NO:168)
34 D---IGYASIGWAVI (SEQ ID NO:142) 13 D---IGTGSVGYACM (SEQ ID NO:169)
50 D---LGTNSIGWCLL (SEQ ID NO:143) 46 D---LGTNSIGSSVR (SEQ ID NO:170)
54 D---LGTNSIGWGLL (SEQ ID NO:144) 60 DIGLRIGIFSCGWSI- (SEQ ID NO:171)
47 D---TGTNSLGWAIV (SEQ ID NO:145) 69 D---MGAKYTGVFYA (SEQ ID NO:172)
49 D---IGTDSIGWAVF (SEQ ID NO:146) 73 D---LGGKNTGFFSF (SEQ ID NO:173)
51 D---LGSTSLGWAIF (SEQ ID NO:147) 74 D---LGVKNTGVFSA (SEQ ID NO:174)
58 D---IGISSIGWAFS (SEQ ID NO:148) 70 D---LGAKFTGVALY (SEQ ID NO:175)
21 D---LGIASVGWCLT (SEQ ID NO:149) 71 D---LGGKFTGVCLS (SEQ ID NO:176)
45 D---LGIASCGWGVV (SEQ ID NO:150) 72 D---LGGTYTGTFIT (SEQ ID NO:177)
18 D---IGSNSIGFAVV (SEQ ID NO:151)                    * *
65 D---IGTTSIGFSVI (SEQ ID NO:152)
29 D---IGITSVGYGLI (SEQ ID NO:153)
30 D---IGITSVGFGII (SEQ ID NO:154)
44 D---LGTTSIGFAHI (SEQ ID NO:155)
27 D---IGIGSVGVGIL (SEQ ID NO:156)
41 D---LGVGSIGVAVA (SEQ ID NO:157)
31 D---VGITSTGYAVL (SEQ ID NO:158)
40 D---LGITSEGYAIL (SEQ ID NO:159)
53 D---IGTSSIGWWLY (SEQ ID NO:160)
55 D---LGSNSLGWFVT (SEQ ID NO:161)
56 D---LGANSLGWFVV (SEQ ID NO:162)
17 D---IGNASVGWSAF (SEQ ID NO:163)
19 D---VGTNSCGWVAM (SEQ ID NO:164)
35 D---VGERSIGLAAV (SEQ ID NO:165)
```

FIG. 4B

ALIGNMENT OF THE HNH-LIKE DOMAINS DISCLOSED IN CHYLINSKI *ET AL.*
(CLUSTAL FORMAT ALIGNMENT BY MAFFT (v7.058b))

```
1    YDIDHIYPRS-LTKD------DSF-DNLVLCERTAN (SEQ ID NO:178)   69  -EIDHALPFS-RTWD------DSF-NNKVLVLASEN (SEQ ID NO:205)
2    -DIDHIYPRSKVIKD------DSF-DNLVLVLKNEN (SEQ ID NO:179)   28  -EIDHIIPIS-ISLD------DSI-NNKVLVLSKAN (SEQ ID NO:206)
3    -DRDHIYPQS-KIKD------DSI-DNLVLVNKTYN (SEQ ID NO:180)   30  -EVDHIIPIS-ISLD------DSI-TNKVLVTHREN (SEQ ID NO:207)
4    -DIDHIYPRS-KIKD------DSI-TNRVLVEKDIN (SEQ ID NO:181)   62  -QVDHALPYS-RSYD------DSK-NNKVLVLTHEN (SEQ ID NO:208)
6    -DIDHIYPQS-KIKD------DSI-SNRVLVCSSCN (SEQ ID NO:182)   27  -EVDHILPLS-ITFD------DSL-ANKVLVYATAN (SEQ ID NO:209)
5    -DIDHIYPQS-KTMD------DSL-NNRVLVKKNYN (SEQ ID NO:183)
7    -DQDHIYPKS-KIYD------DSL-ENRVLVKKNLN (SEQ ID NO:184)
8    -QIDHIVPQS-LVKD------DSF-DNRVLVVPSEN (SEQ ID NO:185)
9    -DIDHIIPQA-FIKD------NSI-DNRVLTSSKEN (SEQ ID NO:186)
12   -DIDHIIPQA-FLKD------NSI-DNKVLVSSASN (SEQ ID NO:187)
16   -DIDHIIPQA-YTKD------NSI-DNRVLVSNITN (SEQ ID NO:188)
11   -DIDHIVPQS-FITD------NSI-DNLVLTSSAGN (SEQ ID NO:189)
10   -DVDHIVPQS-FLKD------DSI-DNKVLTRSDKN (SEQ ID NO:190)
14   -NIDHIYPQS-MVKD------DSL-DNKVLVQSETN (SEQ ID NO:191)
18   -DIDHILPQS-LIKD------DSL-DNEVLVNATIN (SEQ ID NO:192)
19   -DIDHILPQS-FIKD------DSL-ENRVLVKKAVN (SEQ ID NO:193)
13   -EVDHIFPRS-FIKD------DSI-DNKVLVIKKMN (SEQ ID NO:194)
15   -EVDHIIPRS-YIKD------DSF-ENKVLVYREEN (SEQ ID NO:195)
17   -DIDHIIPQA-VTQN------DSI-DNRVLVARAEN (SEQ ID NO:196)
22   -EIDHIIPYS-ISFD------DSS-SNKLLVLAESN (SEQ ID NO:197)
24   -EIDHIIPYS-LCFD------DSS-ANKVLVHKQSN (SEQ ID NO:198)
32   -DIDHIIPYS-RSMD------DSY-SNKVLVLSGEN (SEQ ID NO:199)
63   -DIDHIIPYS-KSMD------DSF-NNKVLCLAEEN (SEQ ID NO:200)
59   -EIDHIYPYS-RSFD------DSY-MNKVLVFTKQN (SEQ ID NO:201)
65   -QIDHIYPYS-RSMD------DSY-MNKVLVLTDEN (SEQ ID NO:202)
64   -EIDHIIPFS-RSFD------DSL-SNKILVLGSEN (SEQ ID NO:203)
68   -EIDHALPFS-RTWD------DSF-NNKVLVLGSEN (SEQ ID NO:204)
```

FIG. 5A

```
26  -EIDHIIPRS-ISFD------DAR-SNKVLVYRSEN (SEQ ID NO:210)  48  -DIEHTIPRS-ISQD------NSQ-MNKTLCSLKFN (SEQ ID NO:237)
29  -EVDHIIPRS-VSFD------NSY-HNKVLVKQSEN (SEQ ID NO:211)  50  -DIDHVIPLA-RGGR------DSL-DNMVLCQSDAN (SEQ ID NO:238)
67  -DIDHILPYS-ITFD------DSF-RNKVLVTSQEN (SEQ ID NO:212)  39  -DIEHLFPIA-ESED------NGR-NNLVISHSACN (SEQ ID NO:239)
58  -EIDHILPRS-RSAD------DSF-ANKVLCLARAN (SEQ ID NO:213)  41  -DVDHIFPRD-DTAD------NSY-GNKVVAHRQCN (SEQ ID NO:240)
51  -EIEHLIPFS-LTLD------DSM-ANKTVCFRQAN (SEQ ID NO:214)  40  -DIEHIVPQS-IGGL------STD-YNTIVTLKSVN (SEQ ID NO:241)
55  -DIDHILPFS-VSLD------DSA-ANKVVCLREAN (SEQ ID NO:215)  35  -EIDHIVPRT-DGGS------NRH-ENLAITCGACN (SEQ ID NO:242)
57  -DIDHLIPFS-ISWD------DSA-ANKVVCMRYAN (SEQ ID NO:216)  36  -EMDHIVPRKGVGST------NTR-TNFAAVCAECN (SEQ ID NO:243)
56  -DIDHILPVA-MTLD------DSP-ANKIICMRYAN (SEQ ID NO:217)  37  -EMDHIVPRKGVGST------NTR-VNLAAACAACN (SEQ ID NO:244)
54  -DVDHILPYS-RTLD------DSF-PNRTLCLREAN (SEQ ID NO:218)  38  -EMDHIVPRAGQGST------NTR-ENLVAVCHRCN (SEQ ID NO:245)
52  -EIEHILPFS-RTLD------DSL-NNRTVAMRRAN (SEQ ID NO:219)  70  -EIDHILPRS-LIKDARGIVFNAE-PNLIYASSRGN (SEQ ID NO:246)
31  -EVDHIIPYS-ISWD------DSY-TNKVLTSAKCN (SEQ ID NO:220)  71  -EIDHIIPRS-ITGRTKKTVFNSE-ANLIYCSSKGN (SEQ ID NO:247)
45  -QVDHILPWS-RFGD------DSY-INKTLCTARSN (SEQ ID NO:221)  73  -EIDHIIPRS-ITLKKSESIYNSE-VNLIFVSAQGN (SEQ ID NO:248)
53  -QVDHILPFS-KTLD------DSF-ANKVLAQHDAN (SEQ ID NO:222)  72  -EIDHIYPRS-ISKKHFGVIFNSE-VNLIYCSSQGN (SEQ ID NO:249)
60  -QIDHAFPLS-RSLD------DSQ-SNKVLCLTSSN (SEQ ID NO:223)
21  -DIDHIVPRS-ISFD------DSF-SNLVIVNKLDN (SEQ ID NO:224)
23  -EIEHIIPYS-MSYD------NSQ-ANKILTEKAEN (SEQ ID NO:225)
25  -EIDHVIPYS-KSAD------DSW-FNKLLVKKSTN (SEQ ID NO:226)
49  -EMDHILPYS-RSLD------NGW-HNRVLVHGKDN (SEQ ID NO:227)
33  -EVDHIVPYS-LILD------NTI-NNKALVIAEEN (SEQ ID NO:228)
42  -EIEHVIPQS-LYFD------DSF-SNKVICEAEVN (SEQ ID NO:229)
43  -DIEHIIPQA-RLFD------DSF-SNKTLEARSVN (SEQ ID NO:230)
44  -EIEHIVPKA-RVFD------DSF-SNKTLTFHRIN (SEQ ID NO:231)
20  -DKDHIIPQS-MKKD------DSIINNLVLVNKNAN (SEQ ID NO:232)
66  -EVEHIWPRS-RSFD------NSP-RNKTLCRKDVN (SEQ ID NO:233)
61  -IVNHIIPYN-RSFD------DTY-HNRVLTLTETK (SEQ ID NO:234)
46  -DMEHTIPKS-ISFD------NSD-QNLTLCESYYN (SEQ ID NO:235)
47  -DIEHTIPRS-AGGD------STK-MNLTLCSSRFN (SEQ ID NO:236)
```

FIG. 5B

```
74   -EIDHILPRS-HTLKIYGTVFNPE-GNLIVHQKCN  (SEQ ID NO:250)
75   -ELDHIIPRS-HKKY---GTLNDE-ANLICVTRGDN (SEQ ID NO:251)
34   -ELEHIVPHS-FRQS-------NAL-SSLVLTWPGVN (SEQ ID NO:252)
          :* *       .   .   :
```

FIG. 5C

ALIGNMENT OF THE HNH-LIKE DOMAINS DISCLOSED IN CHYLINSKI *ET AL.* (EXCLUDING SEQUENCE OUTLIERS).
(CLUSTAL FORMAT ALIGNMENT BY MAFFT (v7.058b))

1	YDIDHIYPRS-LTKDDS-FDNLVLCERTAN	(SEQ ID NO:253)	31	-EVDHIIPYS-ISWDDS-YTNKVLTSAKCN (SEQ ID NO:280)
2	-DIDHIYPRSKVIKDDS-FDNLVLVLKNEN	(SEQ ID NO:254)	32	-DIDHIIPYS-RSMDDS-YSNKVLVLSGEN (SEQ ID NO:281)
3	-DRDHIYPQS-KIKDDS-IDNLVLVNKTYN	(SEQ ID NO:255)	23	-EIEHIIPYS-MSYDNS-QANKILTEKAEN (SEQ ID NO:282)
4	-DIDHIYPRS-KIKDDS-ITNEVLVEKDIN	(SEQ ID NO:256)	33	-EVDHIVPYS-LILDNT-INNKALVYAEEN (SEQ ID NO:283)
6	-DIDHIYPQS-KIKDDS-ISNRVLVCSSCN	(SEQ ID NO:257)	25	-EIDEVIPYS-KSADDS-WFNKLLVKKSTN (SEQ ID NO:284)
5	-DIDHIYPQS-KTMDDS-LNNRVLVKKNYN	(SEQ ID NO:258)	49	-EMDHILPYS-RSLDNG-WHNRVLVHGKDN (SEQ ID NO:285)
7	-DQDHIYPKS-KIYDDS-LENRVLVKKNLN	(SEQ ID NO:259)	42	-EIEHVIPQS-LYFDDS-FSNKVICEAEVN (SEQ ID NO:286)
8	-QIDHIVPQS-LVKDDS-FDNRVLVVPSEN	(SEQ ID NO:260)		
9	-DIDHIIPQA-FIKDNS-IDNRVLTSSKEN	(SEQ ID NO:261)		
12	-DIDHIIPQA-FLKDNS-IDNKVLVSSASN	(SEQ ID NO:262)		
16	-DIDHIIPQA-YTKDNS-LDNRVLVSNITN	(SEQ ID NO:263)		
11	-DIDHIVPQS-FITDNS-IDNLVLTSSAGN	(SEQ ID NO:264)		
10	-DVDHIVPQS-FLKDDS-IDNKVLTRSDKN	(SEQ ID NO:265)		
14	-NIDHIYPQS-MVKDDS-LDNKVLVQSEIN	(SEQ ID NO:266)		
18	-DIDHILPQS-LIKDDS-LDNRVLVNATIN	(SEQ ID NO:267)		
19	-DIDHILPQS-FIKDDS-LENRVLVKKAVN	(SEQ ID NO:268)		
13	-EVDHIFPRS-FIKDDS-IDNKVLVIKKMN	(SEQ ID NO:269)		
15	-EVDHIIPRS-YIKDDS-FENKVLVYREEN	(SEQ ID NO:270)		
17	-DIDHIIPQA-VTQNDS-IDNRVLVARAEN	(SEQ ID NO:271)		
21	-DIDHIVPRS-ISFDDS-FSNLVTVNKLDN	(SEQ ID NO:272)		
22	-EIDHIIPYS-ISFDDS-SSNKLLVLAESN	(SEQ ID NO:273)		
24	-EIDHIIPYS-LCFDDS-SANKVLVHKQSN	(SEQ ID NO:274)		
28	-EIDHIIPIS-ISLDDS-INNKVLVLSKAN	(SEQ ID NO:275)		
30	-EVDHIIPIS-ISLDDS-ITNKVLVTHREN	(SEQ ID NO:276)		
27	-EVDHILPLS-ITFDDS-LANKVLVYATAN	(SEQ ID NO:277)		
26	-EIDHIIPRS-ISFDDA-RSNKVLVYRSEN	(SEQ ID NO:278)		
29	-EVDHIIPRS-VSFDNS-YHNKVLVKQSEN	(SEQ ID NO:279)		

FIG. 6A

```
43  -DIEHIIPQA-RLFDDS-FSNKTLEARSVN  (SEQ ID NO:287)
44  -EIEHIVPKA-RVFDDS-FSNKTLTFHRIN  (SEQ ID NO:288)
20  -DKDHIIPQS-MKKDDSIINNLVLVNKNAN  (SEQ ID NO:289)
45  -QVDHILPWS-RFGDDS-YLNKTLCTARSN  (SEQ ID NO:290)
50  -DIDHVIPLA-RGGRDS-LDNMVLCQSDAN  (SEQ ID NO:291)
46  -DMEHTIPKS-ISFDNS-DQNLTLCESYYN  (SEQ ID NO:292)
47  -DIEHTIPRS-AGGDST-KMNLTLCSSRFN  (SEQ ID NO:293)
48  -DIEHTIPRS-ISQDNS-QMNKTLCSLKFN  (SEQ ID NO:294)
39  -DIEHLFPIA-ESEDNG-RNNLVISHSACN  (SEQ ID NO:295)
41  -DVDHIFPRD-DTADNS-YGNKVVAHRQCN  (SEQ ID NO:296)
40  -DIEHIVPQS-LGGLST-DYNTIVTLKSVN  (SEQ ID NO:297)
35  -ELDHIVPRT-DGGSNR-HENLAITCGACN  (SEQ ID NO:298)
36  -EMDHIVPRKGVGSTNT-RTNFAAVCAECN  (SEQ ID NO:299)
37  -EMDHIVPRKGVGSTNT-RVNLAAACAACN  (SEQ ID NO:300)
38  -EMDHIVPRAGQGSTNT-RENLVAVCHRCN  (SEQ ID NO:301)
34  -ELEHIVPES-FRQSNA-LSSLVLTWPGVN  (SEQ ID NO:302)
      : :* *   .    .
```

FIG. 6B

SEQUENCE ALIGNMENT BETWEEN SpCas9 AND NmCas9

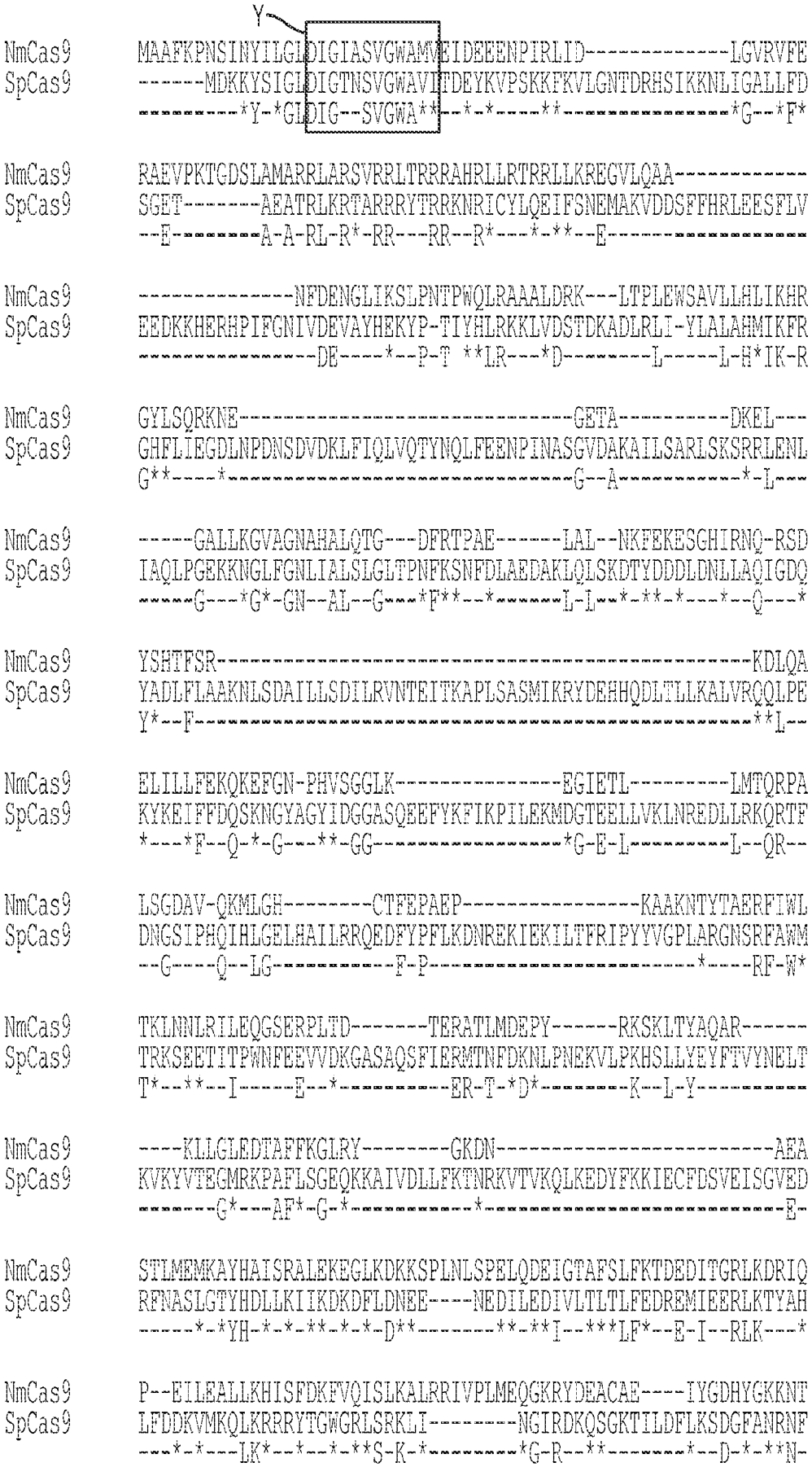


FIG. 7A

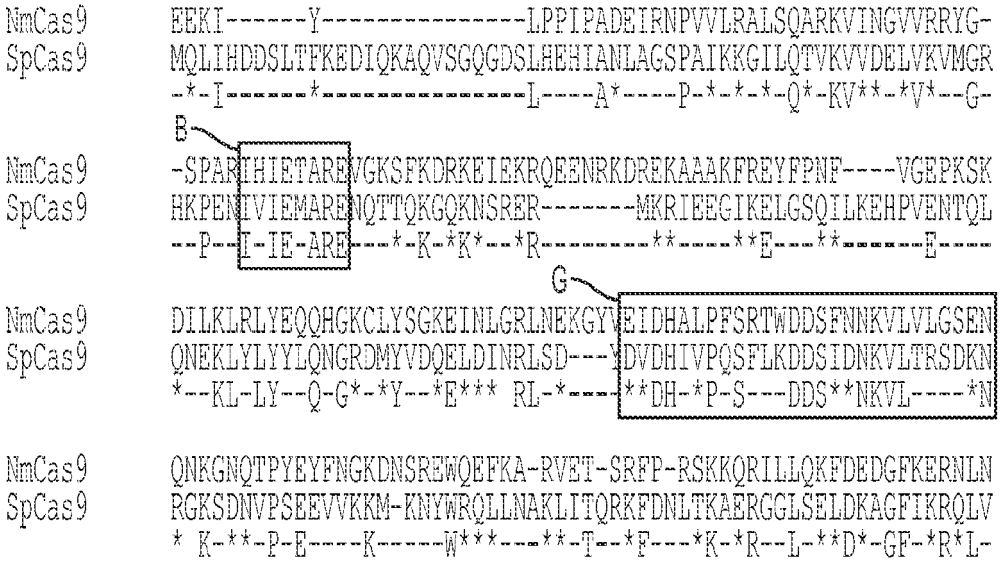
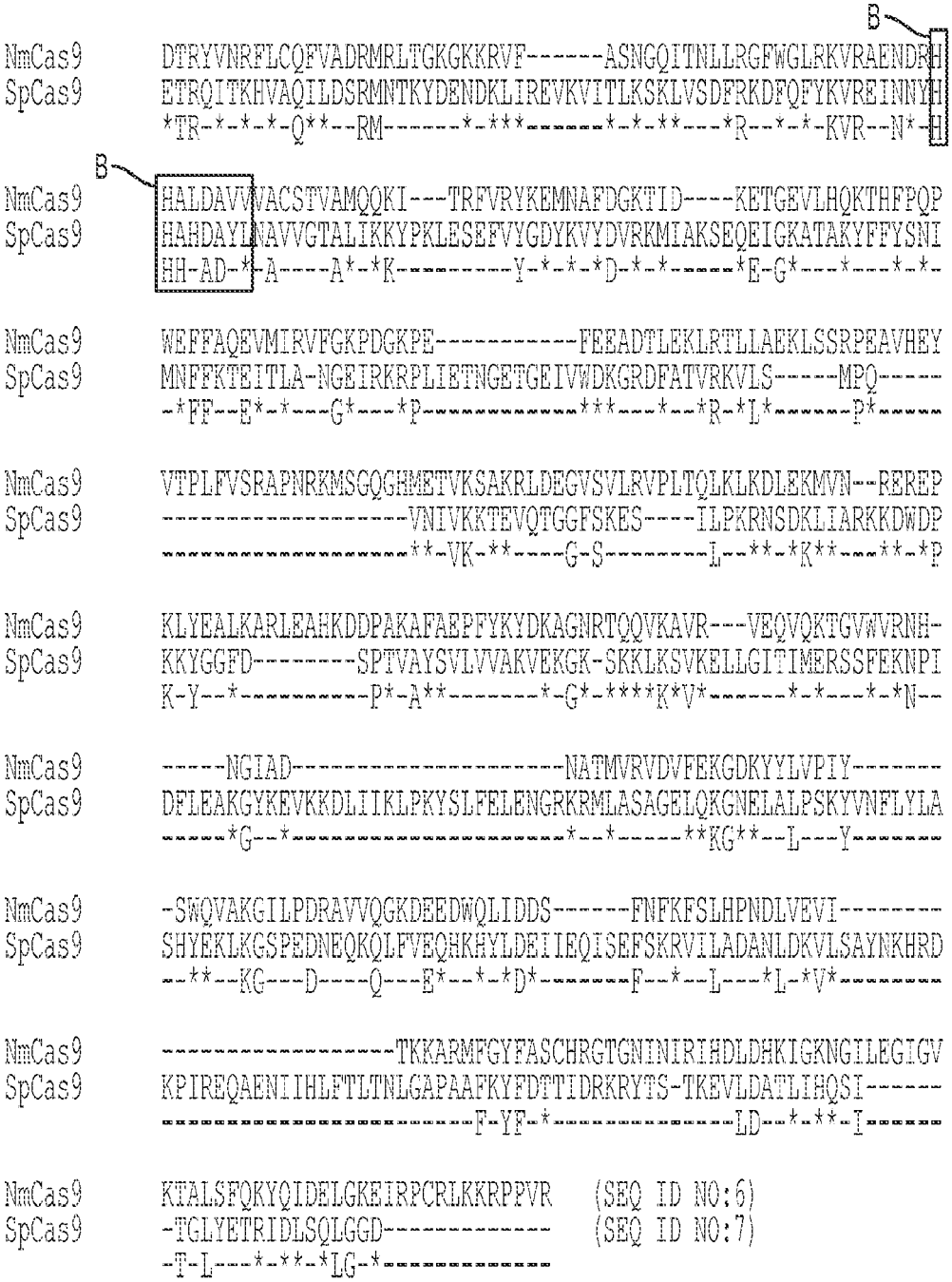


FIG. 7A

CONTINUED



PERCENT IDENTITY MATRIX - CREATED BY CLUSTAL2.1

FIG. 7B

SEQUENCE OF THE NmCas9 ORF WITH DUAL NLS AND HA TAGS



R: SV40 NLS, G: HA TAG, O: SYNTHETIC NLS (1); ALL ELSE NmCas9

FIG. 8

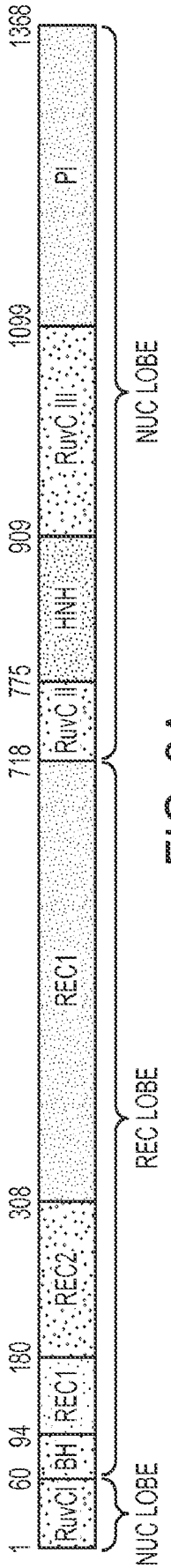

1
60
94
180
308
718
775
909
1099
1368
RuvCI
BH
REC1
REC2
REC1
RuvC II
HNH
RuvC III
PI
NUC LOBE
REC LOBE
NUC LOBE

FIG. 9A

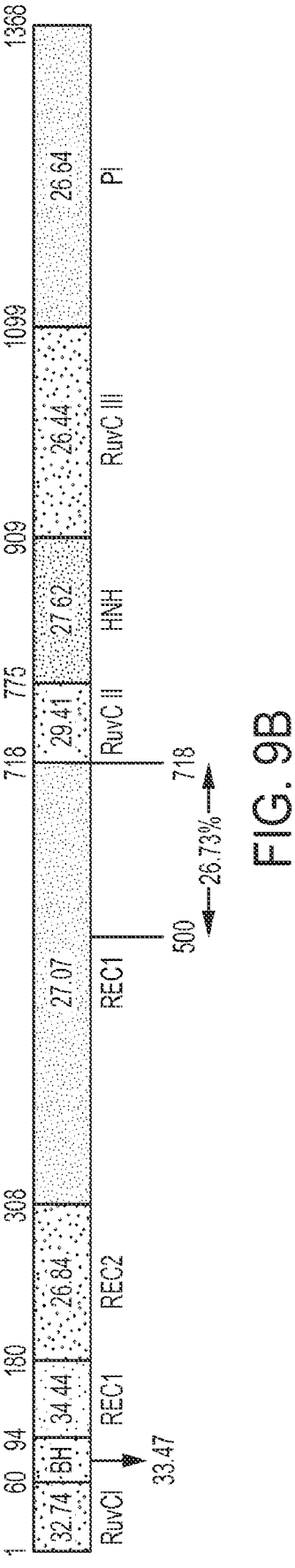

1
60
94
180
308
718
775
909
1099
1368
32.74
BH
34.44
26.84
27.07
29.41
27.62
26.44
26.64
RuvCI
REC1
REC2
REC1
RuvC II
HNH
RuvC III
PI
33.47
500
718
26.73%

FIG. 9B

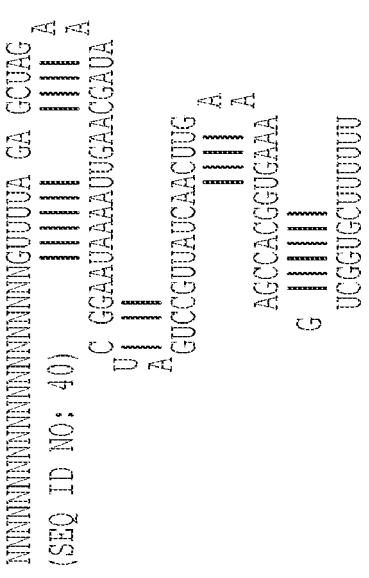


FIG. 10A

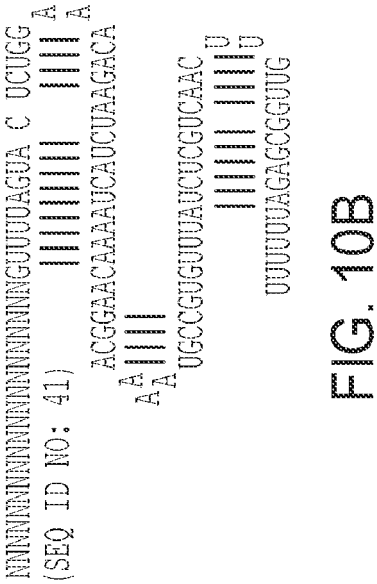


FIG. 10B

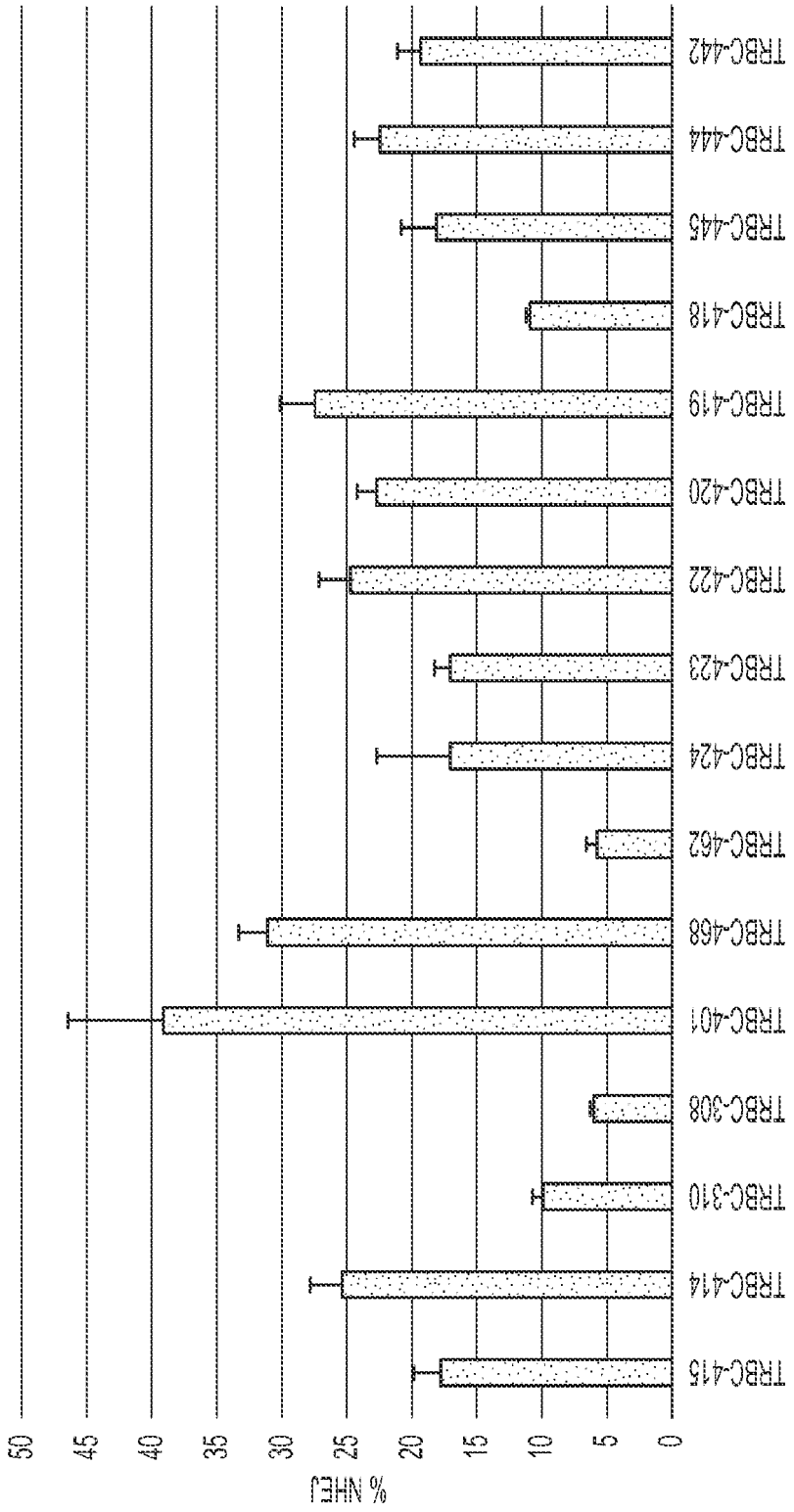

TRBC-442
TRBC-444
TRBC-445
TRBC-418
TRBC-419
TRBC-420
TRBC-422
TRBC-423
TRBC-424
TRBC-462
TRBC-468
TRBC-401
TRBC-308
TRBC-310
TRBC-414
TRBC-415
0
5
10
15
20
25
30
35
40
45
50
% NHEJ

FIG. 11

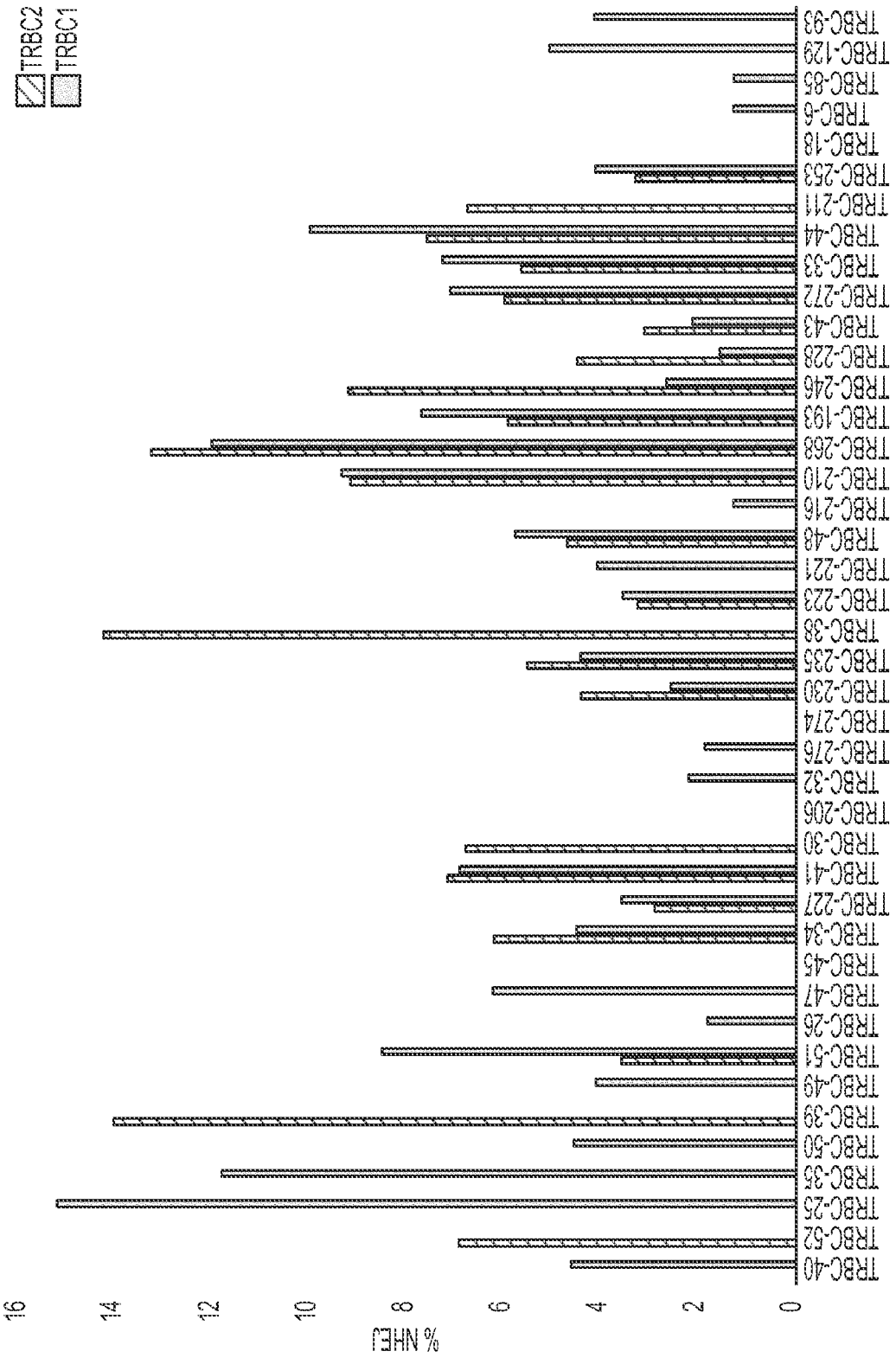

TRBC2
TRBC1
% NHEJ
0
2
4
6
8
10
12
14
16
TRBC-40
TRBC-52
TRBC-25
TRBC-35
TRBC-50
TRBC-39
TRBC-49
TRBC-51
TRBC-26
TRBC-47
TRBC-45
TRBC-34
TRBC-227
TRBC-41
TRBC-30
TRBC-206
TRBC-32
TRBC-276
TRBC-274
TRBC-230
TRBC-235
TRBC-38
TRBC-223
TRBC-221
TRBC-48
TRBC-216
TRBC-210
TRBC-268
TRBC-193
TRBC-246
TRBC-228
TRBC-43
TRBC-272
TRBC-33
TRBC-44
TRBC-211
TRBC-253
TRBC-18
TRBC-6
TRBC-85
TRBC-129
TRBC-93

FIG. 12

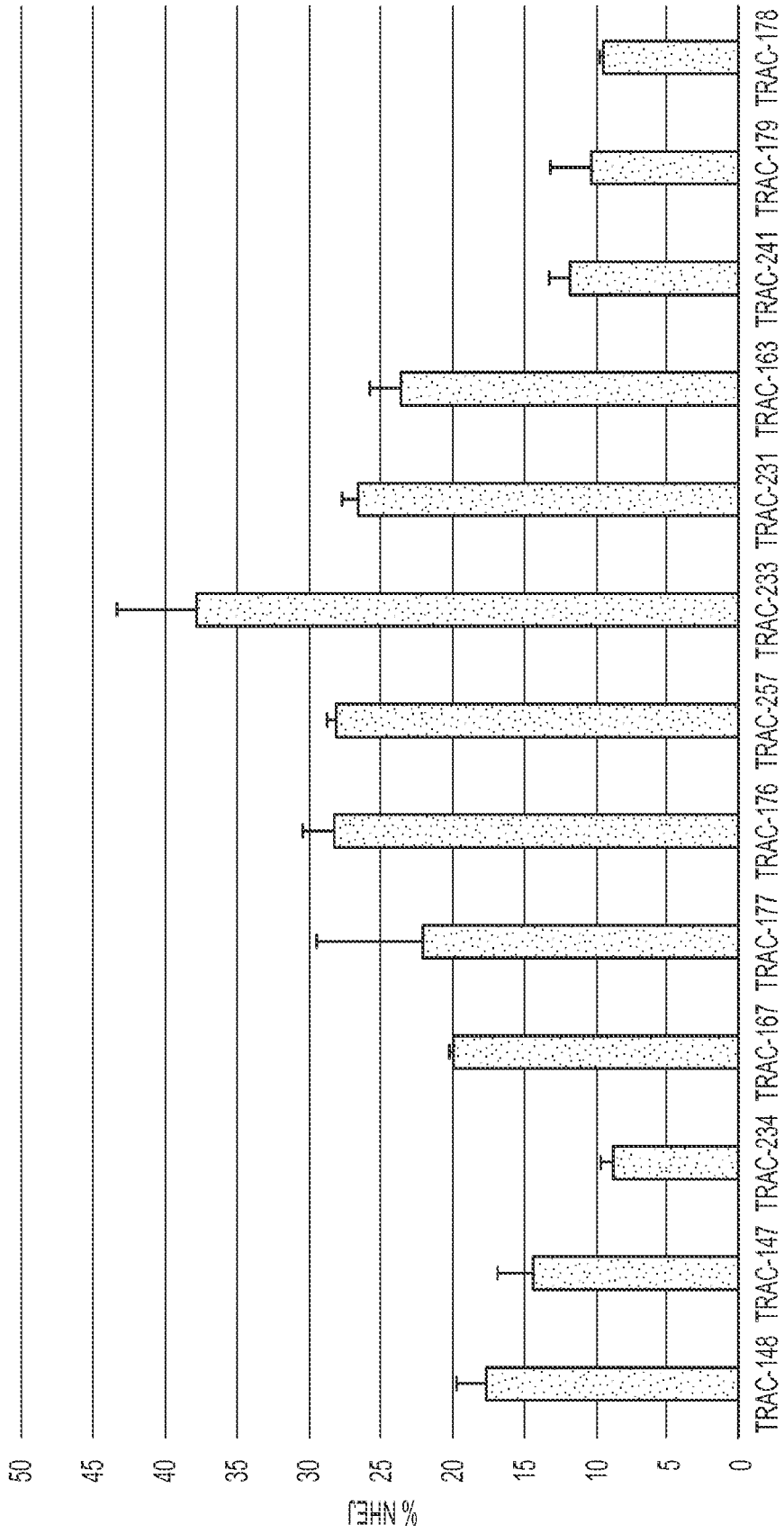

INDEL %
50
45
40
35
30
25
20
15
10
5
0
TRAC-148
TRAC-147
TRAC-234
TRAC-167
TRAC-177
TRAC-176
TRAC-257
TRAC-233
TRAC-231
TRAC-163
TRAC-241
TRAC-179
TRAC-178

FIG. 13

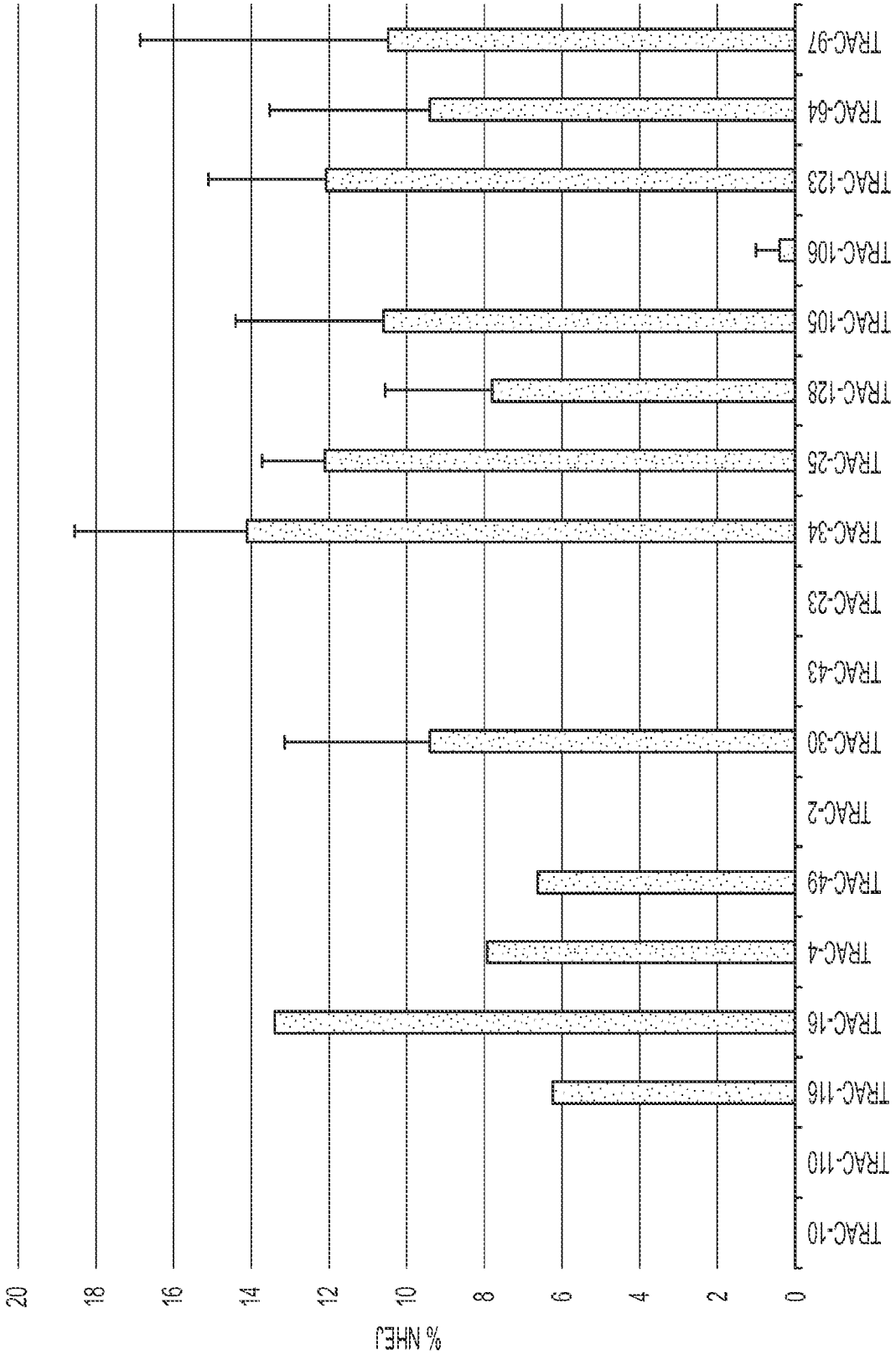

TRAC-97
TRAC-64
TRAC-123
TRAC-106
TRAC-105
TRAC-128
TRAC-25
TRAC-34
TRAC-23
TRAC-43
TRAC-30
TRAC-2
TRAC-49
TRAC-4
TRAC-16
TRAC-116
TRAC-110
TRAC-10
0
2
4
6
8
10
12
14
16
18
20
% NHEJ

FIG. 14

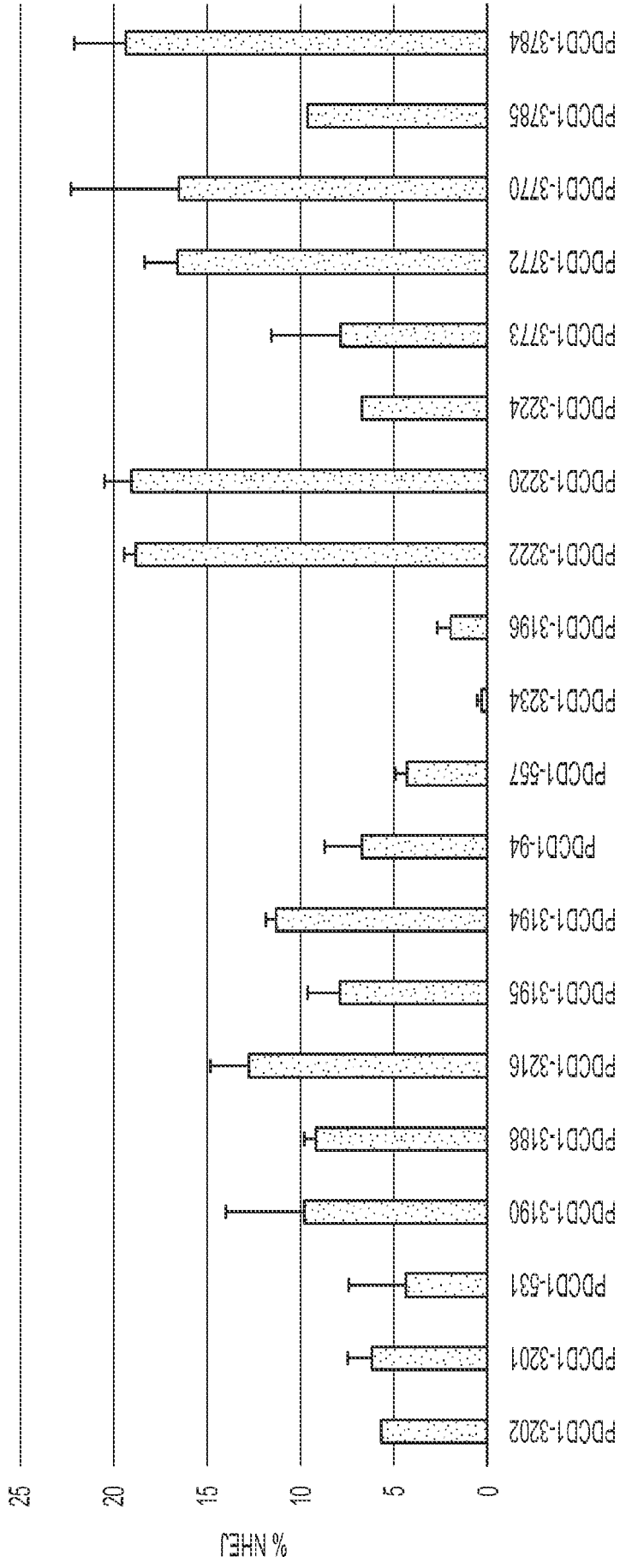

PDCD1-3784
PDCD1-3785
PDCD1-3770
PDCD1-3772
PDCD1-3773
PDCD1-3224
PDCD1-3220
PDCD1-3222
PDCD1-3196
PDCD1-3234
PDCD1-557
PDCD1-94
PDCD1-3194
PDCD1-3195
PDCD1-3216
PDCD1-3188
PDCD1-3190
PDCD1-531
PDCD1-3201
PDCD1-3202
gRNA
25
20
15
10
5
0
% NHEJ

FIG. 15

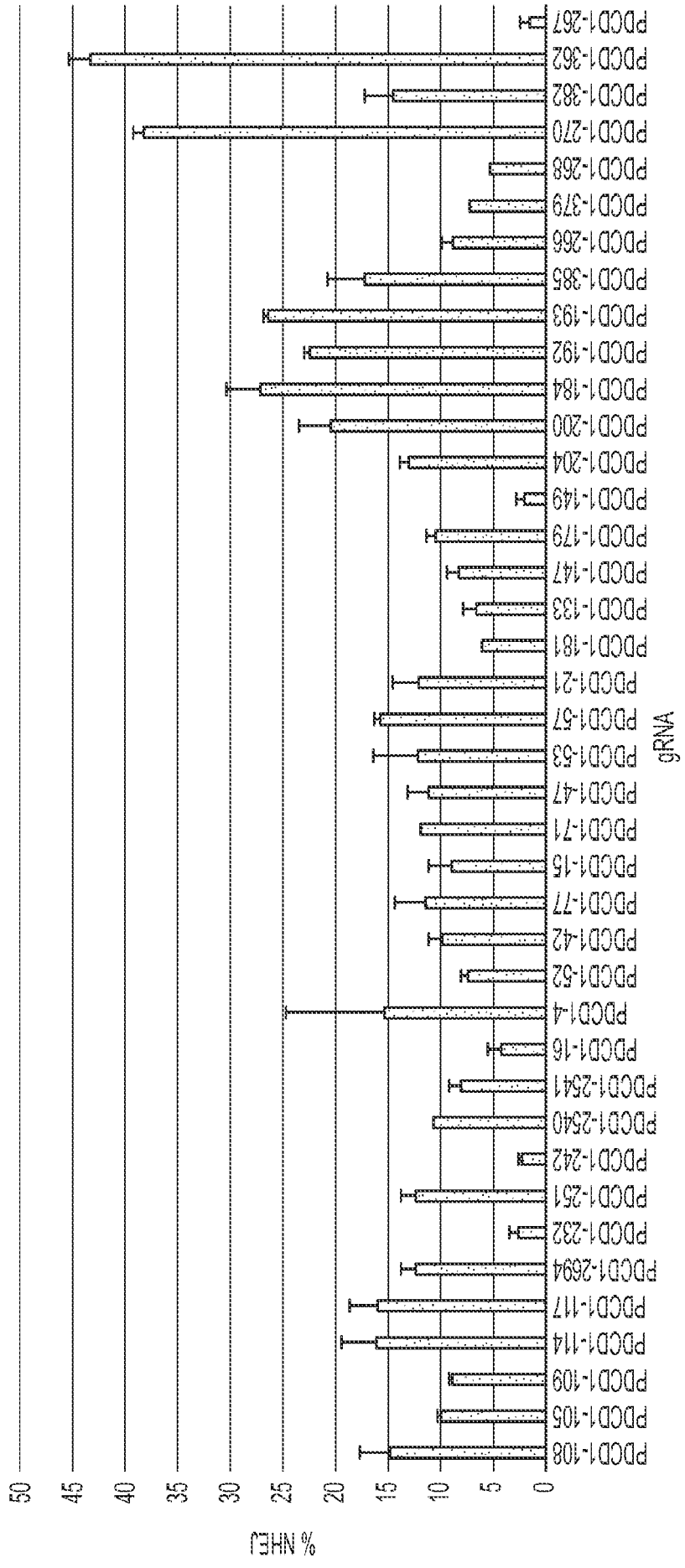

% NHEJ
0
5
10
15
20
25
30
35
40
45
50
gRNA
PDCD1-108
PDCD1-105
PDCD1-109
PDCD1-114
PDCD1-117
PDCD1-2694
PDCD1-232
PDCD1-251
PDCD1-242
PDCD1-2540
PDCD1-2541
PDCD1-16
PDCD1-4
PDCD1-52
PDCD1-42
PDCD1-77
PDCD1-15
PDCD1-71
PDCD1-47
PDCD1-53
PDCD1-57
PDCD1-21
PDCD1-181
PDCD1-133
PDCD1-147
PDCD1-179
PDCD1-149
PDCD1-204
PDCD1-200
PDCD1-184
PDCD1-192
PDCD1-193
PDCD1-385
PDCD1-266
PDCD1-379
PDCD1-268
PDCD1-270
PDCD1-382
PDCD1-362
PDCD1-267

FIG. 16

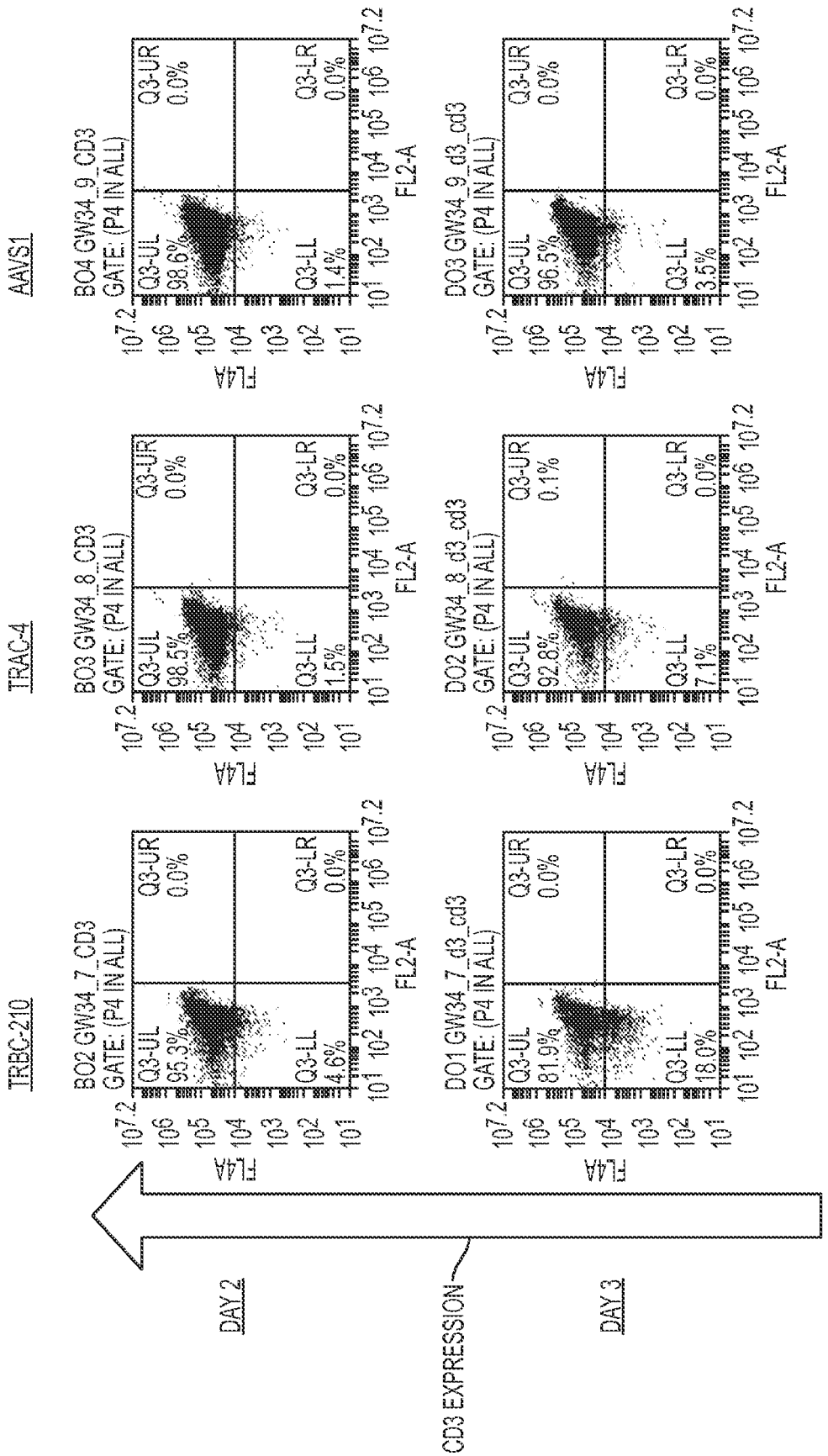

TRBC-210
TRAC-4
AAVS1
DAY 2
DAY 3
CD3 EXPRESSION
BO2 GW34_7_CD3
GATE: (P4 IN ALL)
Q3-UL 95.3%
Q3-UR 0.0%
Q3-LL 4.6%
Q3-LR 0.0%
DO1 GW34_7_d3_cd3
GATE: (P4 IN ALL)
Q3-UL 81.9%
Q3-UR 0.0%
Q3-LL 18.0%
Q3-LR 0.0%
BO3 GW34_8_CD3
GATE: (P4 IN ALL)
Q3-UL 98.5%
Q3-UR 0.0%
Q3-LL 1.5%
Q3-LR 0.0%
DO2 GW34_8_d3_cd3
GATE: (P4 IN ALL)
Q3-UL 92.8%
Q3-UR 0.1%
Q3-LL 7.1%
Q3-LR 0.0%
BO4 GW34_9_CD3
GATE: (P4 IN ALL)
Q3-UL 98.6%
Q3-UR 0.0%
Q3-LL 1.4%
Q3-LR 0.0%
DO3 GW34_9_d3_cd3
GATE: (P4 IN ALL)
Q3-UL 96.5%
Q3-UR 0.0%
Q3-LL 3.5%
Q3-LR 0.0%
FL4A
FL2-A

FIG. 17A

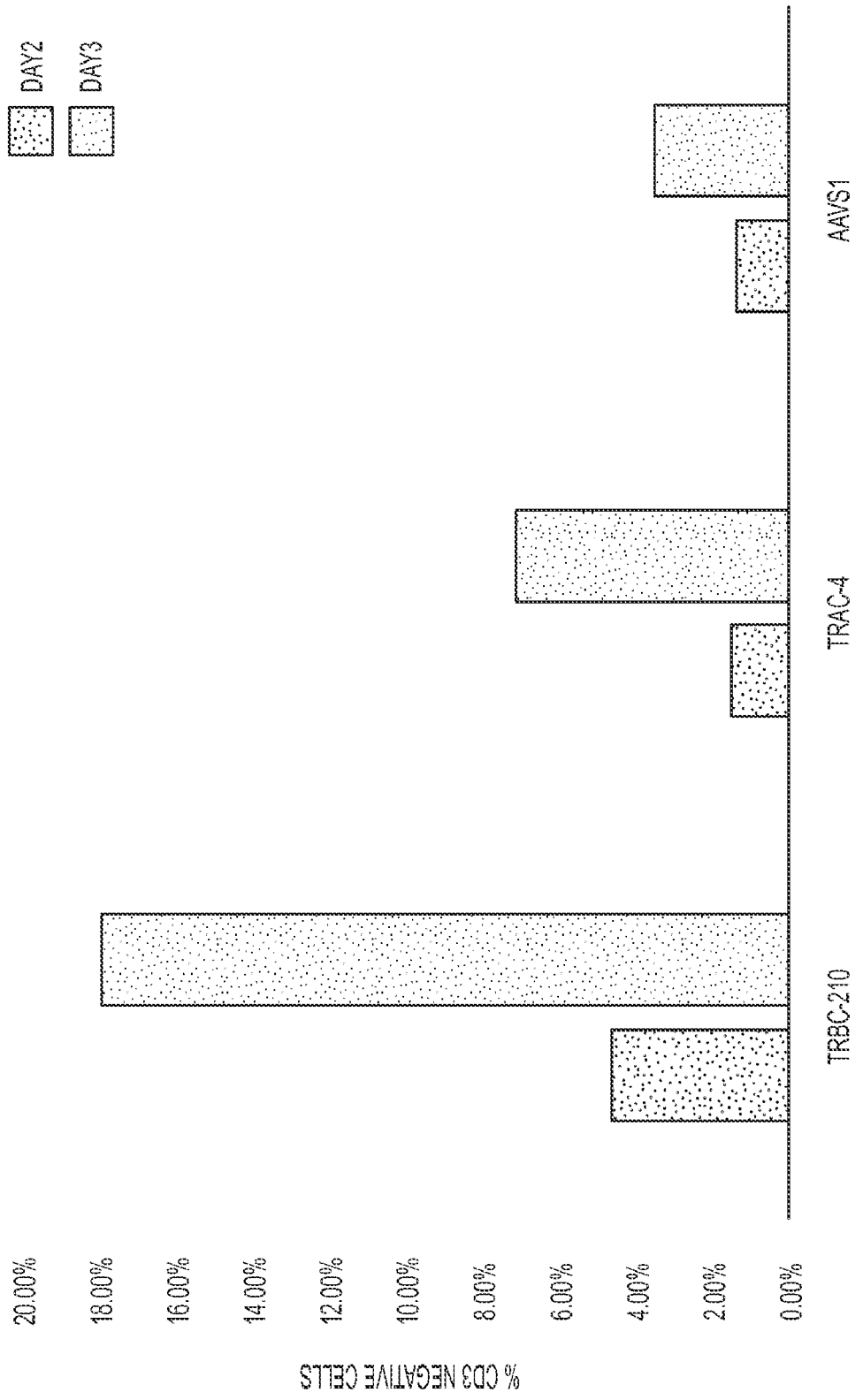

DAY2
DAY3
% CD3 NEGATIVE CELLS
20.00%
18.00%
16.00%
14.00%
12.00%
10.00%
8.00%
6.00%
4.00%
2.00%
0.00%
TRBC-210
TRAC-4
AAVS1

FIG. 17B

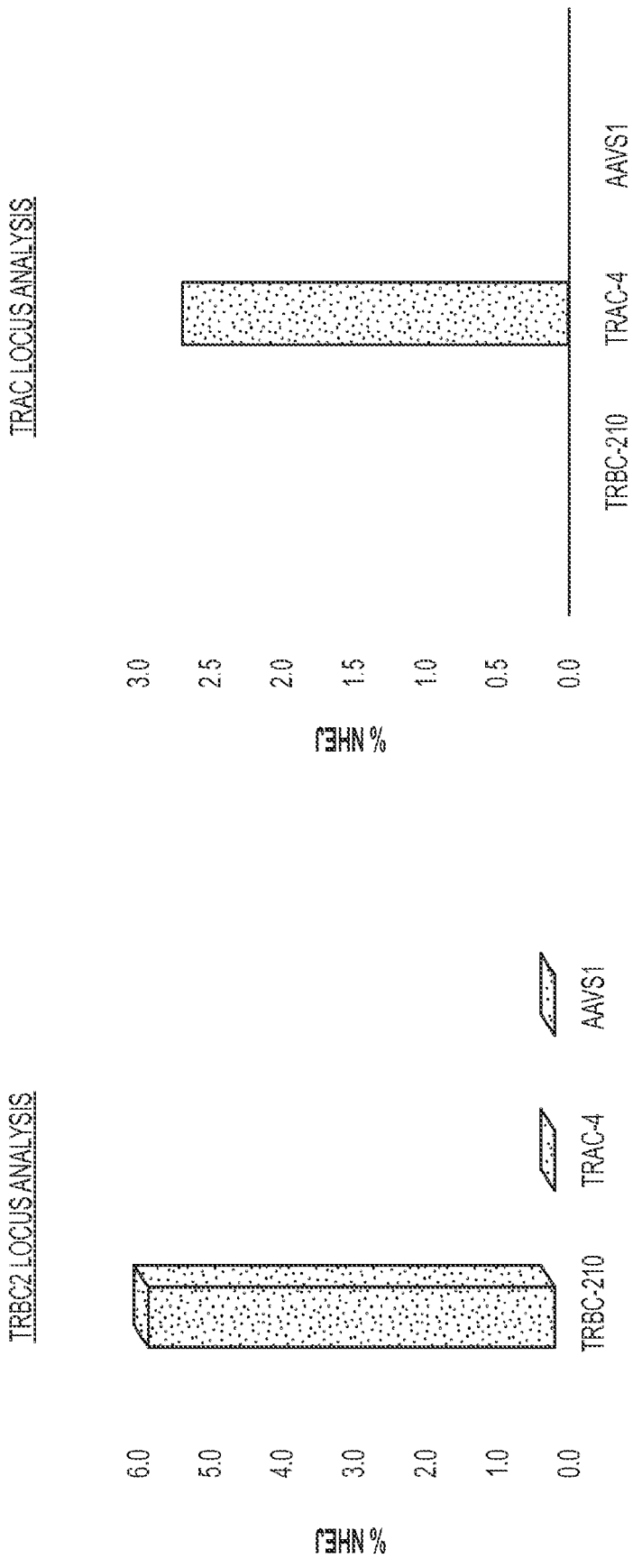

TRAC LOCUS ANALYSIS
AAVS1
TRAC-4
TRBC-210
0.0
0.5
1.0
1.5
2.0
2.5
3.0
INDEL %
TRBC2 LOCUS ANALYSIS
AAVS1
TRAC-4
TRBC-210
0.0
1.0
2.0
3.0
4.0
5.0
6.0
INDEL %

FIG. 17C

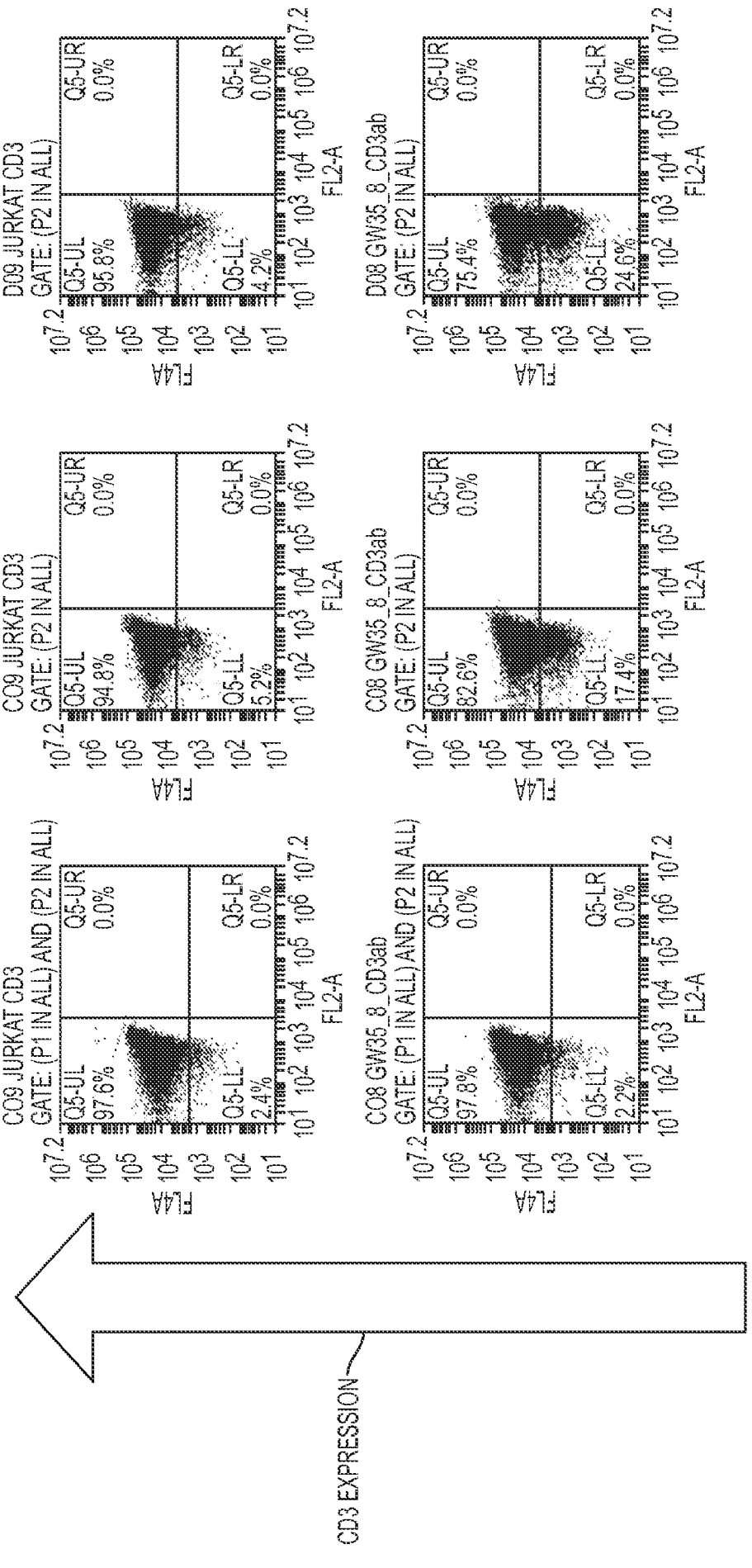

DAY 1
DAY 1
DAY 3
CO9 JURKAT CD3
GATE: (P1 IN ALL) AND (P2 IN ALL)
Q5-UL 97.6%
Q5-LL 2.4%
Q5-UR 0.0%
Q5-LR 0.0%
CO8 GW35_8_CD3ab
GATE: (P1 IN ALL) AND (P2 IN ALL)
Q5-UL 97.8%
Q5-LL 2.2%
Q5-UR 0.0%
Q5-LR 0.0%
CO9 JURKAT CD3
GATE: (P2 IN ALL)
Q5-UL 94.8%
Q5-LL 5.2%
Q5-UR 0.0%
Q5-LR 0.0%
CO8 GW35_8_CD3ab
GATE: (P2 IN ALL)
Q5-UL 82.6%
Q5-LL 17.4%
Q5-UR 0.0%
Q5-LR 0.0%
D09 JURKAT CD3
GATE: (P2 IN ALL)
Q5-UL 95.8%
Q5-LL 4.2%
Q5-UR 0.0%
Q5-LR 0.0%
D08 GW35_8_CD3ab
GATE: (P2 IN ALL)
Q5-UL 75.4%
Q5-LL 24.6%
Q5-UR 0.0%
Q5-LR 0.0%
FL4A
FL2-A
CD3 EXPRESSION

FIG. 18A

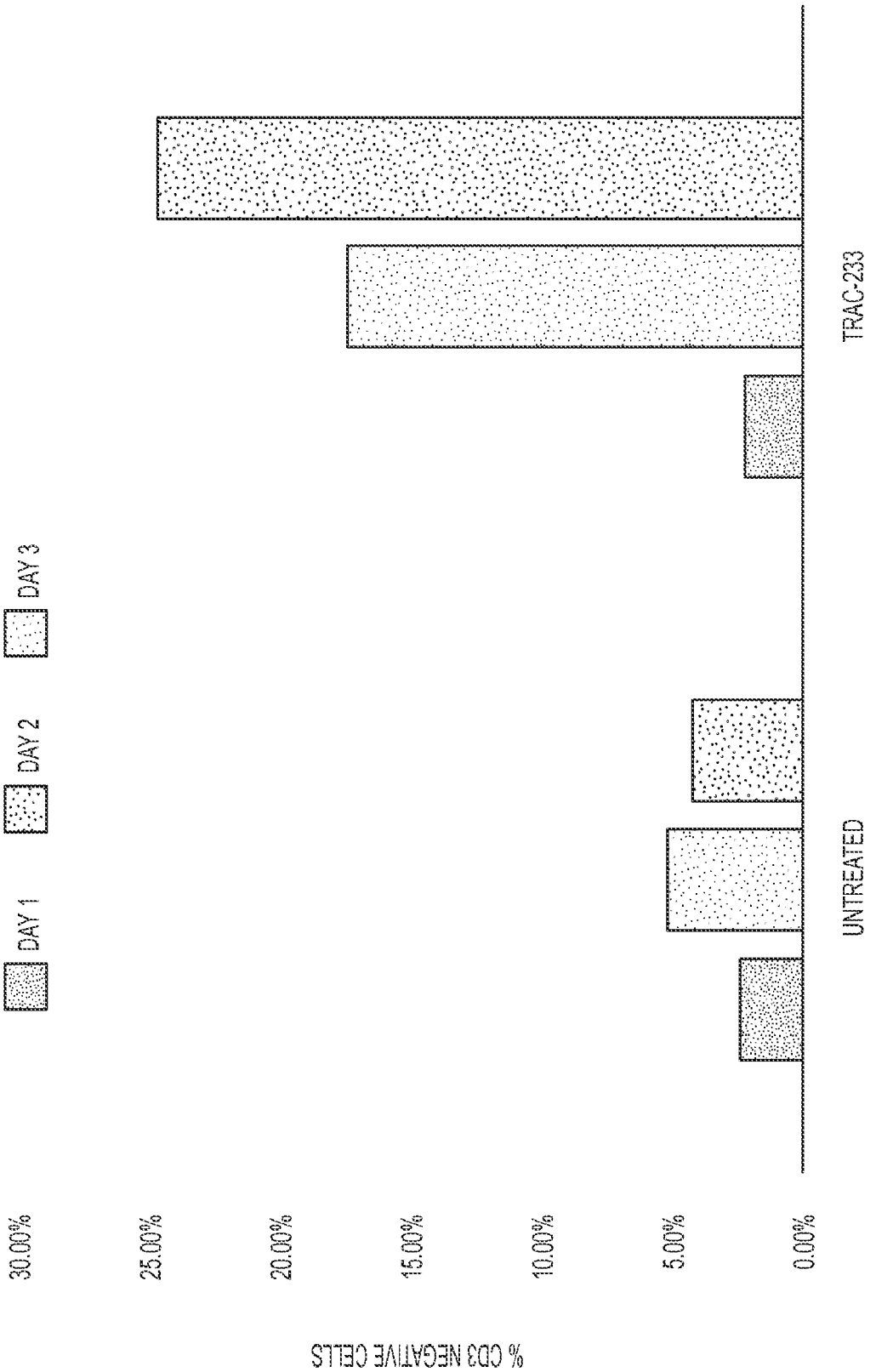

% CD3 NEGATIVE CELLS
30.00%
25.00%
20.00%
15.00%
10.00%
5.00%
0.00%
DAY 1
DAY 2
DAY 3
UNTREATED
TRAC-233

FIG. 18B

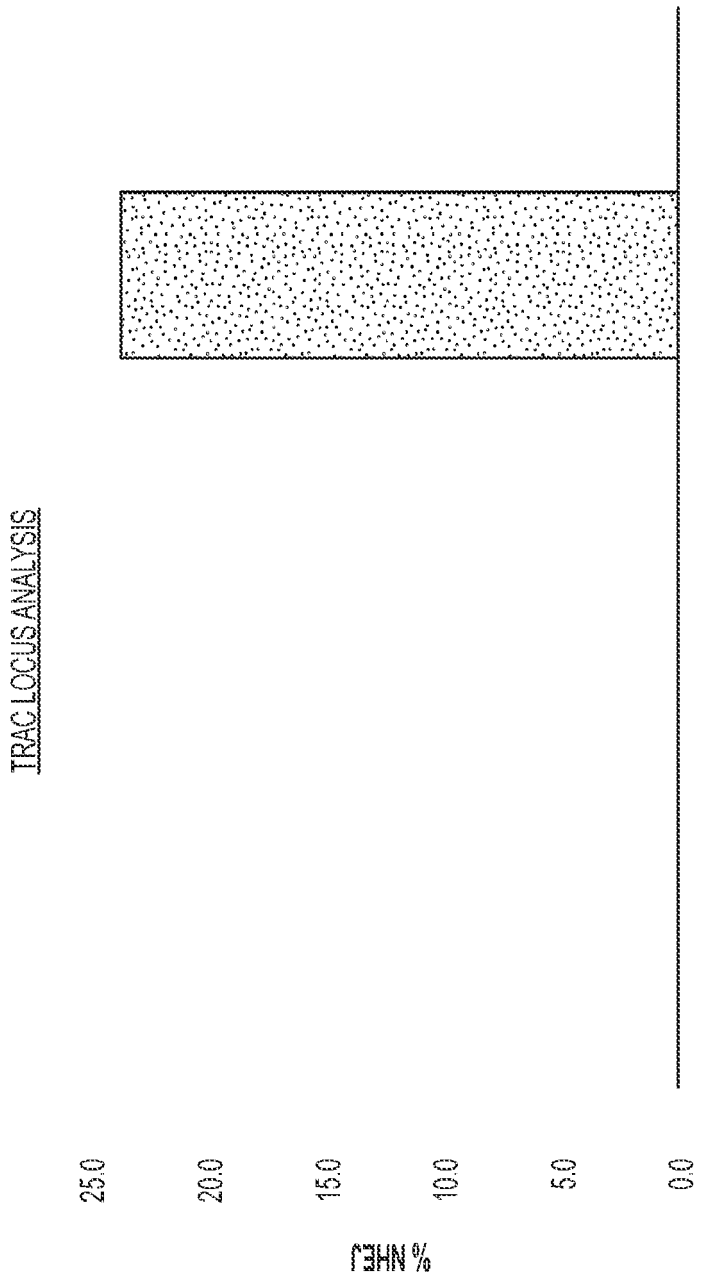

TRAC LOCUS ANALYSIS
INDEL %
25.0
20.0
15.0
10.0
5.0
0.0
UNTREATED
TRAC-233

FIG. 18C

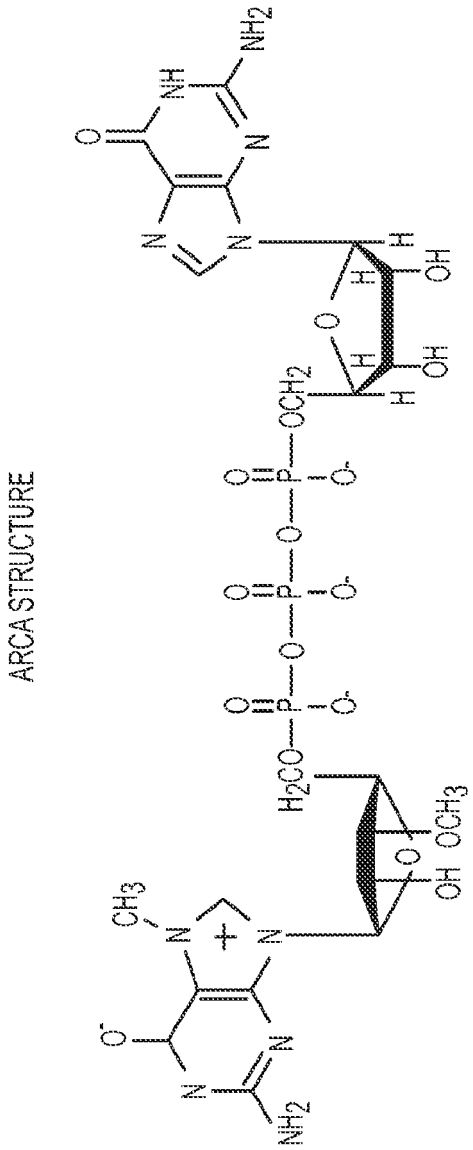

ARCA STRUCTURE
NH2
NH
O
N
N
N
H
H
OH
O
H
OH
H
OCH2
O
P
O-
O
P
O-
O
P
O-
H2CO
O
OH
OCH3
CH3
N
+
N
O-
N
N
NH2

FIG. 19

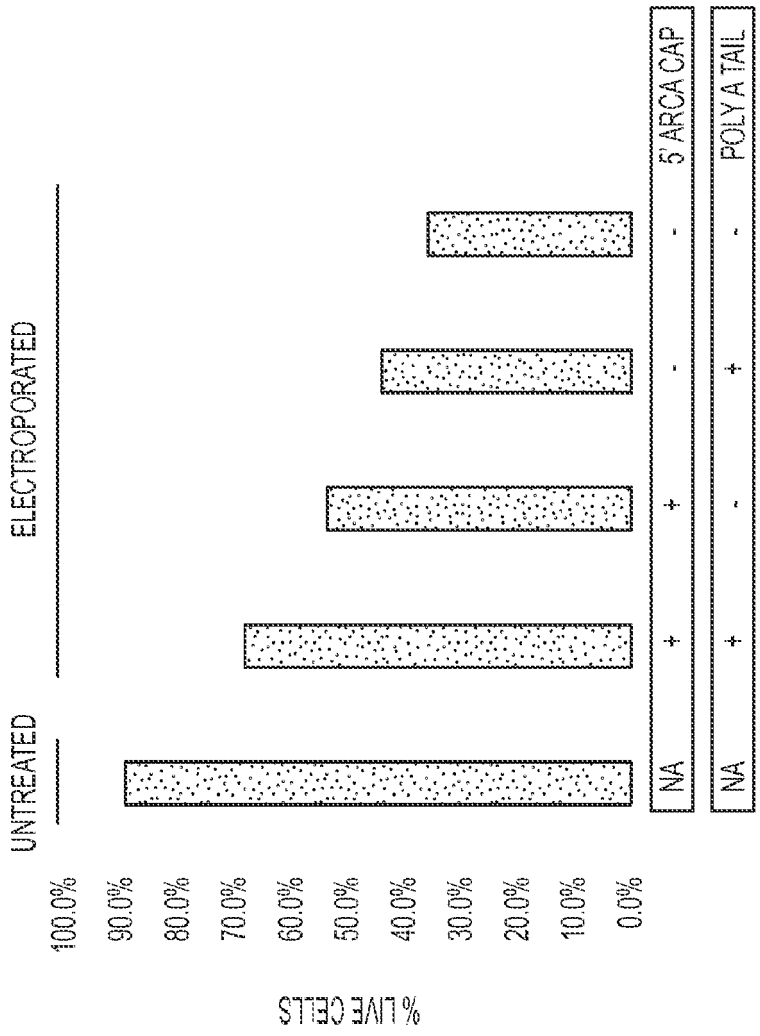

% LIVE CELLS
100.0%
90.0%
80.0%
70.0%
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
UNTREATED
ELECTROPORATED
NA
+
+
-
-
NA
+
-
+
-
5' ARCA CAP
POLY A TAIL

FIG. 20

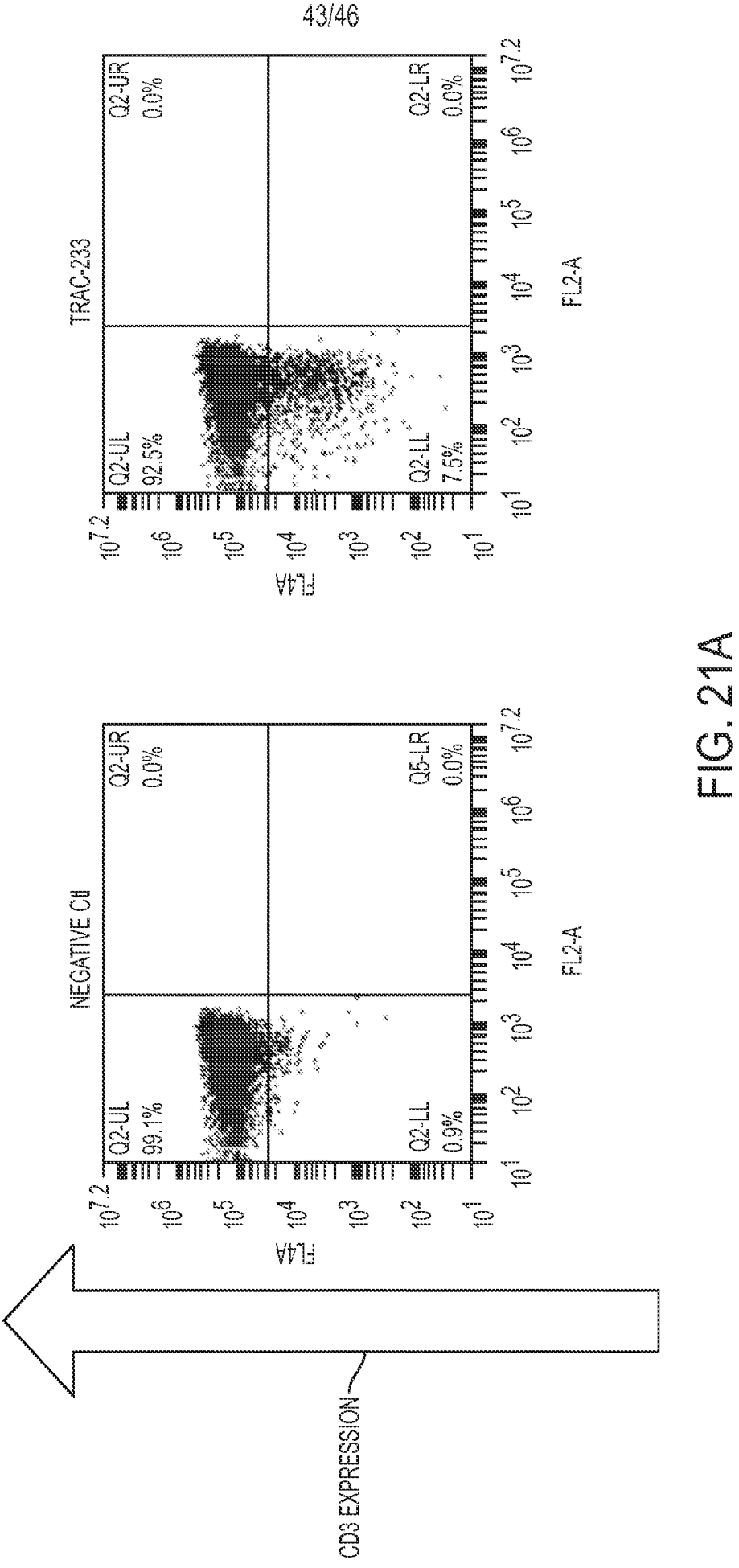

TRAC-233
Q2-UR
0.0%
Q2-LR
0.0%
Q2-UL
92.5%
Q2-LL
7.5%
FL4A
FL2-A
NEGATIVE CTL
Q2-UR
0.0%
Q5-LR
0.0%
Q2-UL
99.1%
Q2-LL
0.9%
FL4A
FL2-A
CD3 EXPRESSION

FIG. 21A

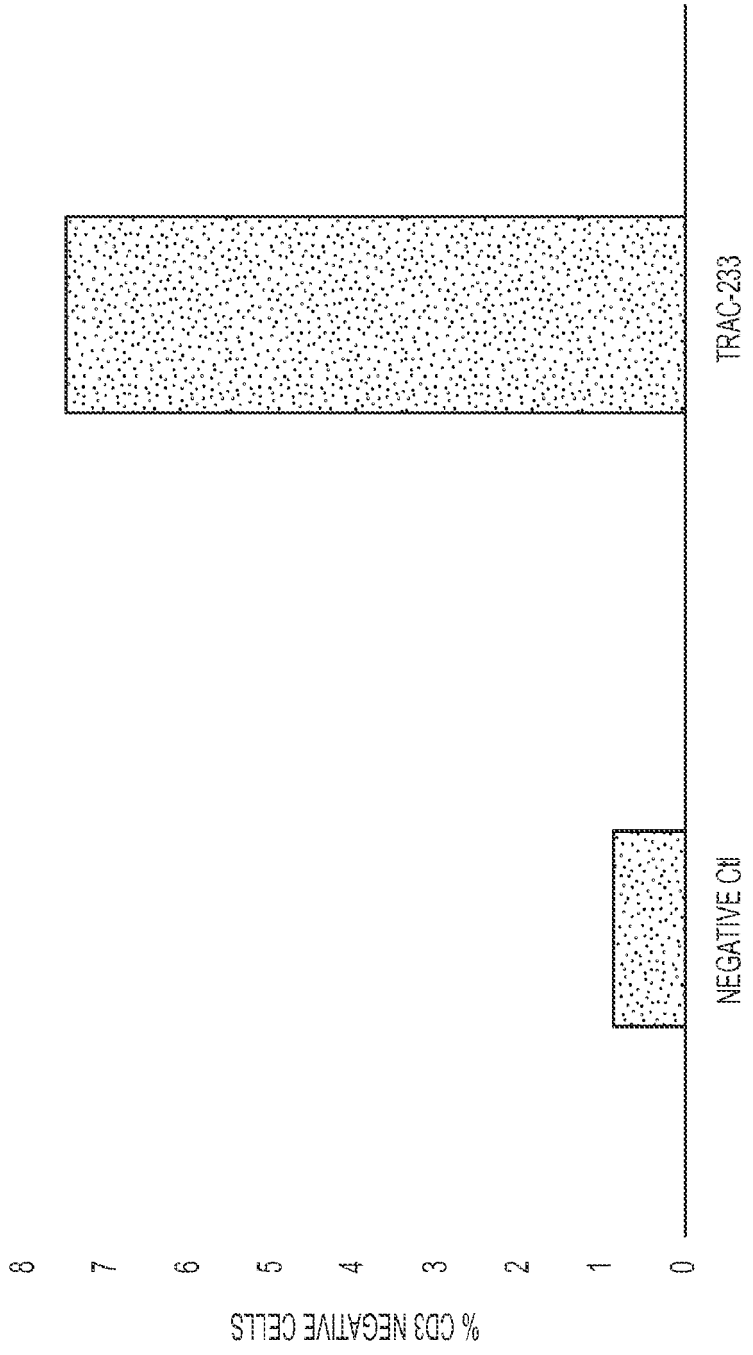


FIG. 21B

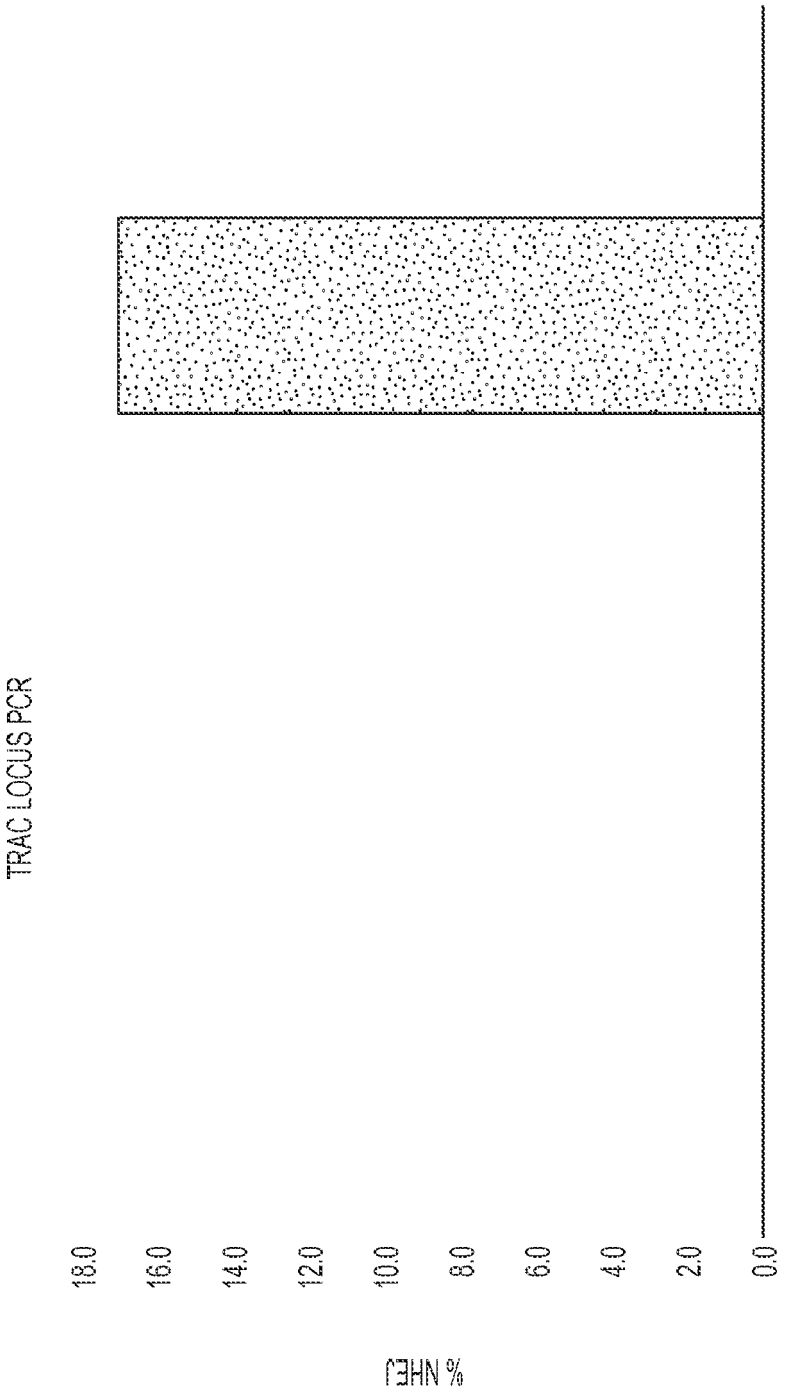

TRAC LOCUS PCR
% NHEJ
18.0
16.0
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
NEGATIVE Ctl
TRAC-233

FIG. 21C

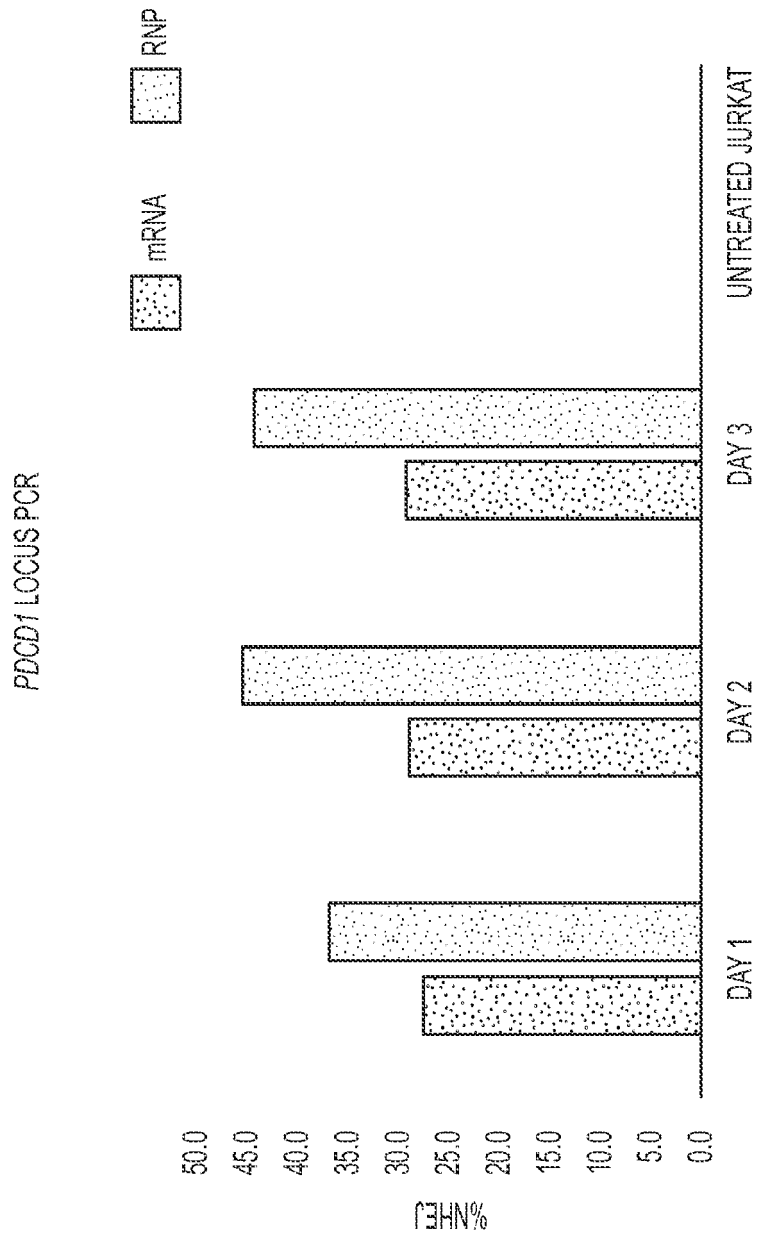

PDCD1 LOCUS PCR
mRNA
RNP
UNTREATED JURKAT
DAY 3
DAY 2
DAY 1
50.0
45.0
40.0
35.0
30.0
25.0
20.0
15.0
10.0
5.0
0.0
%INDEL

FIG. 22