

LISTADO DE SECUENCIAS

<110> INTELLIA THERAPEUTICS, INC.

<120> COMPOSICIONES Y MÉTODOS PARA LA EDICIÓN DEL GEN TTR Y EL TRATAMIENTO DE LA AMILOIDOSIS ATTR

<130> 01155-0013-00PCT

<150> US 62/566,236

<151> 2017-09-29

<150> US 62/671,902

<151> 2018-05-15

<160> 278

<170> PatentIn version 3.5

<210> 1

<211> 4411

<212> ADN

<213> Secuencia artificial

<220>

<223> Sintético: transcrito de Cas9 con 5 UTR de HSD, ORF correspondiente a la SEQ ID NO: 204, secuencia de Kozak, y 3 UTR de ALB

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- <223> Sintético: secuencia modificada de ARNsg
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<213> Secuencia artificial

<220>

<223> Sintético: ARNg CR003361 dirigido a TTR humana (Exón 3)

<400> 31

gcugcauggg cucacaacug 20

<210> 32

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

<223> Sintético: ARNg CR003362 dirigido a TTR humana (Exón 3)

<400> 32

gcaugggcuc acaacugagg 20

<210> 33

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

<223> Sintético: ARNg CR003363 dirigido a TTR humana (Exón 3)

<400> 33

acugaggagg aauuuguaga 20

<210> 34

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

<223> Sintético: ARNg CR003364 dirigido a TTR humana (Exón 3)

<400> 34

cugaggagga auuuguagaa 20

<210> 35

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

<223> Sintético: ARNg CR003365 dirigido a TTR humana (Exón 3)

<400> 35

uguagaaggg auauacaaag 20

<210> 36

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

<223> Sintético: ARNg CR003366 dirigido a TTR humana (Exón 3)

<400> 36
aaauagacac caaauuuac 20

<210> 37
<211> 20
<212> ARN
<213> Secuencia artificial

<220>

<223> Sintético: ARNg CR003367 dirigido a TTR humana (Exón 3)

<400> 37
agacacaaa uuuuacugga 20

<210> 38
<211> 20
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<213> Secuencia artificial

<220>

<223> Sintético: ARNg CR003368 dirigido a TTR humana (Exón 3)

<400> 38
aagugccuuc caguaagauu 20

<210> 39
<211> 20
<212> ARN
<213> Secuencia artificial

<220>

<223> Sintético: ARNg CR003369 dirigido a TTR humana (Exón 3)

<400> 39
cucugcaugc ucauggaaug 20

<210> 40
<211> 20
<212> ARN
<213> Secuencia artificial

<220>

<223> Sintético: ARNg CR003370 dirigido a TTR humana (Exón 3)

<400> 40
ccucugcaug cucauggaau 20

<210> 41
<211> 20

<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: ARNg CR003371 dirigido a TTR humana (Exón 3)

<400> 41
accucugcau gcucauggaa 20

<210> 42
<211> 20
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: ARNg CR003372 dirigido a TTR humana (Exón 3)

<400> 42
uacucaccuc ugcaugcuca 20

<210> 43
<211> 20
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: ARNg CR003373 dirigido a TTR humana (Exón 4)

<400> 43
guauucacag ccaacgacuc 20

<210> 44
<211> 20
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: ARNg CR003374 dirigido a TTR humana (Exón 4)

<400> 44
gcggcggggg ccggagucgu 20

<210> 45
<211> 20
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: ARNg CR003375 dirigido a TTR humana (Exón 4)

<400> 45
aaugguguag cggcgggggc 20

<210> 46

<211> 20
 <212> ARN
 <213> Secuencia artificial

 <220>
 <223> Sintético: ARNg CR003376 dirigido a TTR humana (Exón 4)

 <400> 46
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 <210> 47
 <211> 20
 <212> ARN
 <213> Secuencia artificial

 <220>
 <223> Sintético: ARNg CR003377 dirigido a TTR humana (Exón 4)

 <400> 47
 gcggcaaugg uguagcggcg 20

 <210> 48
 <211> 20
 <212> ARN
 <213> Secuencia artificial

 <220>
 <223> Sintético: ARNg CR003378 dirigido a TTR humana (Exón 4)

 <400> 48
 ggcggcaaug gugagcggc 20

 <210> 49
 <211> 20
 <212> ARN
 <213> Secuencia artificial

 <220>
 <223> Sintético: ARNg CR003379 dirigido a TTR humana (Exón 4)

 <400> 49
 gggcggcaau gguguagcgg 20

 <210> 50
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 <212> ARN
 <213> Secuencia artificial

 <220>
 <223> Sintético: ARNg CR003380 dirigido a TTR humana (Exón 4)

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<210> 51
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 <212> ARN
 <213> Secuencia artificial

 <220>
 <223> Sintético: ARNg CR003381 dirigido a TTR humana (Exón 4)

 <400> 51
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 <210> 52
 <211> 20
 <212> ARN
 <213> Secuencia artificial

 <220>
 <223> Sintético: ARNg CR003382 dirigido a TTR humana (Exón 4)

 <400> 52
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 <210> 53
 <211> 20
 <212> ARN
 <213> Secuencia artificial

 <220>
 <223> Sintético: ARNg CR003383 dirigido a TTR humana (Exón 4)

 <400> 53
 auaggaguag gggcucagca 20

 <210> 54
 <211> 20
 <212> ARN
 <213> Secuencia artificial

 <220>
 <223> Sintético: ARNg CR003384 dirigido a TTR humana (Exón 4)

 <400> 54
 aaauaggagua ggggcucagc 20

 <210> 55
 <211> 20
 <212> ARN
 <213> Secuencia artificial

 <220>
 <223> Sintético: ARNg CR003385 dirigido a TTR humana (Exón 4)

 <400> 55
 ccccuacucc uauuccacca 20

<210> 56
<211> 20
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: ARNg CR003386 dirigido a TTR humana (Exón 4)

<400> 56
ccguggugga auaggaguag 20

<210> 57
<211> 20
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: ARNg CR003387 dirigido a TTR humana (Exón 4)

<400> 57
gccguggugg aauaggagua 20

<210> 58
<211> 20
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: ARNg CR003388 dirigido a TTR humana (Exón 4)

<400> 58
gacgacagcc gugguggaau 20

<210> 59
<211> 20
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: ARNg CR003389 dirigido a TTR humana (Exón 4)

<400> 59
auuggugacg acagccgugg 20

<210> 60
<211> 20
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: ARNg CR003390 dirigido a TTR humana (Exón 4)

<400> 60
gggauuggug acgacagccg 20

<210> 61
<211> 20
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: ARNg CR003391 dirigido a TTR humana (Exón 4)

<400> 61
ggcugucguc accaauccca 20

<210> 62
<211> 20
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: ARNg CR003392 dirigido a TTR humana (Exón 4)

<400> 62
agucccucau uccuugggau 20

<210> 63
<211> 20
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: ARNg CR005298 dirigido a TTR humana (Exón 1)

<400> 63
uccacucauu cuuggcagga 20

<210> 64
<211> 20
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: ARNg CR005299 dirigido a TTR humana (Exón 4)

<400> 64
agccguggug gaauaggagu 20

<210> 65
<211> 20
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: ARNg CR005300 dirigido a TTR humana (Exón 1)

<400> 65

ucacagaaac acucaccgua20

<210> 66<211> 20<212> ARN<213> Secuencia artificial<220><223> Sintético: ARNg CR005301 dirigido a TTR humana (Exón 1)<400> 66gucacagaaa cacucaccgu20

<210> 67<211> 20<212> ARN<213> Secuencia artificial<220><223> Sintético: ARNg CR005302 dirigido a TTR humana (Exón 2)<400> 67acgugucuuc ucuacacca20

<210> 68<211> 20<212> ARN<213> Secuencia artificial<220><223> Sintético: ARNg CR005303 dirigido a TTR humana (Exón 2)<400> 68ugaauccaag uguccucuga20

<210> 69<211> 20<212> ARN<213> Secuencia artificial<220><223> Sintético: ARNg CR005304 dirigido a TTR humana (Exón 2)<400> 69ggccgugcau guguucagaa20

<210> 70<211> 20<212> ARN<213> Secuencia artificial<220><223> Sintético: ARNg CR005305 dirigido a TTR humana (Exón 3)

<400> 70	
uauaggaaaa ccagugaguc	20
<210> 71	
<211> 20	
<212> ARN	
<213> Secuencia artificial	
<220>	
<223> Sintético: ARNg CR005306 dirigido a TTR humana (Exón 3)	
<400> 71	
aaaucuuacu ggaaggcacu	20
<210> 72	
<211> 20	
<212> ARN	
<213> Secuencia artificial	
<220>	
<223> Sintético: ARNg CR005307 dirigido a TTR humana (Exón 4)	
<400> 72	
ugucugucuu cucucauagg	20
<210> 73	
<211> 20	
<212> ARN	
<213> Secuencia artificial	
<220>	
<223> Sintético: ARNg CR000689 dirigido a TTR de cyno	
<400> 73	
acacaaauac caguccagcg	20
<210> 74	
<211> 20	
<212> ARN	
<213> Secuencia artificial	
<220>	
<223> Sintético: ARNg CR005364 dirigido a TTR de cyno	
<400> 74	
aaaggcugcu gaugagaccu	20
<210> 75	
<211> 20	
<212> ARN	
<213> Secuencia artificial	
<220>	
<223> Sintético: ARNg CR005365 dirigido a TTR de cyno	

<400> 75
cauugacagc aggacugccu 20

<210> 76
<211> 20
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: ARNg CR005366 dirigido a TTR de cyno

<400> 76
auaccagucc agcgaggcag 20

<210> 77
<211> 20
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: ARNg CR005367 dirigido a TTR de cyno

<400> 77
ccaguccagc gaggcagagg 20

<210> 78
<211> 20
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: ARNg CR005368 dirigido a TTR de cyno

<400> 78
ccuccucugc cucgcuggac 20

<210> 79
<211> 20
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: ARNg CR005369 dirigido a TTR de cyno

<400> 79
aaaguucuag augccguccg 20

<210> 80
<211> 20
<212> ARN
<213> Secuencia artificial

<220>

<223> Sintético: ARNg CR005370 dirigido a TTR de cyno

<400> 80
acuugucuuc ucuauaccca 20

<210> 81
<211> 20
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: ARNg CR005371 dirigido a TTR de cyno

<400> 81
aagugacuuc caguaagauu 20

<210> 82
<211> 20
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: ARNg CR005372 dirigido a TTR de cyno

<400> 82
aaaaggcugc ugaugagacc 20

<210> 83

<400> 83
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<210> 84

<400> 84
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<210> 85

<400> 85
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<210> 86

<400> 86
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<210> 87
<211> 100
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: secuencia modificada de ARNsg G000480 dirigido a TTR humana

<220>
<221> base_modificada
<222> (1)..(3)
<223> Enlace PS, nucleótido 2'-O-Me

<220>
<221> base_modificada
<222> (29)..(40)
<223> nucleótido 2'-O-Me

<220>
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<222> (69)..(96)
<223> nucleótido 2'-O-Me

<220>
<221> base_modificada
<222> (97)..(100)
<223> Enlace PS, nucleótido 2'-O-Me

<400> 87
aaaggcugcu gaugacaccu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguaaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 88
<211> 100
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: secuencia modificada de ARNsg G000481 dirigido a TTR humana

<220>
<221> base_modificada
<222> (1)..(3)
<223> Enlace PS, nucleótido 2'-O-Me

<220>
<221> base_modificada
<222> (29)..(40)
<223> nucleótido 2'-O-Me

<220>
<221> base_modificada
<222> (69)..(96)
<223> nucleótido 2'-O-Me

<220>
<221> base_modificada
<222> (97)..(100)
<223> Enlace PS, nucleótido 2'-O-Me

<400> 88
ucuagaacuu ugaccaucag guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguaaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 89
<211> 100
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: secuencia modificada de ARNsg G000482 dirigido a TTR humana

<220>
<221> base_modificada
<222> (1)..(3)
<223> Enlace PS, nucleótido 2'-O-Me

<220>
<221> base_modificada
<222> (29)..(40)
<223> nucleótido 2'-O-Me

<220>
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<222> (69)..(96)
<223> nucleótido 2'-O-Me

<220>
<221> base_modificada
<222> (97)..(100)
<223> Enlace PS, nucleótido 2'-O-Me

<400> 89
uguagaagg g auauacaaag guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguaaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 90
<211> 100
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: secuencia modificada de ARNsg G000483 dirigido a TTR humana

<220>
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<222> (1)..(3)
<223> Enlace PS, nucleótido 2'-O-Me

<220>
<221> base_modificada
<222> (29)..(40)
<223> nucleótido 2'-O-Me

<220>
<221> base_modificada
<222> (69)..(96)

<223> nucleótido 2'-O-Me

<220>
<221> base_modificada
<222> (97)..(100)
<223> Enlace PS, nucleótido 2'-O-Me

<400> 90
uccacucauu cuuggcagga guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 91
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<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: secuencia modificada de ARNsg G000484 dirigido a TTR humana

<220>
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<222> (1)..(3)
<223> Enlace PS, nucleótido 2'-O-Me

<220>
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<223> nucleótido 2'-O-Me

<220>
<221> base_modificada
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<223> nucleótido 2'-O-Me

<220>
<221> base_modificada
<222> (97)..(100)
<223> Enlace PS, nucleótido 2'-O-Me

<400> 91
agacaccaaa ucuuacugga guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 92
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<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: secuencia modificada de ARNsg G000485 dirigido a TTR humana

<220>
<221> base_modificada

<222> (1)..(3)
<223> Enlace PS, nucleótido 2'-O-Me

<220>
<221> base_modificada
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<223> nucleótido 2'-O-Me

<220>
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<222> (69)..(96)
<223> nucleótido 2'-O-Me

<220>
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<222> (97)..(100)
<223> Enlace PS, nucleótido 2'-O-Me

<400> 92
ccuccucugc cuugcuggac guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguaaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 93
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<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: secuencia modificada de ARNsg G000486 dirigido a TTR humana

<220>
<221> base_modificada
<222> (1)..(3)
<223> Enlace PS, nucleótido 2'-O-Me

<220>
<221> base_modificada
<222> (29)..(40)
<223> nucleótido 2'-O-Me

<220>
<221> base_modificada
<222> (69)..(96)
<223> nucleótido 2'-O-Me

<220>
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<222> (97)..(100)
<223> Enlace PS, nucleótido 2'-O-Me

<400> 93
acacaaauac caguccagca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguaaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 94
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<220>
<223> Sintético: secuencia modificada de ARNsg G000487 dirigido a TTR humana

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<222> (1)..(3)
<223> Enlace PS, nucleótido 2'-O-Me

<220>
<221> base_modificada
<222> (29)..(40)
<223> nucleótido 2'-O-Me

<220>
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<222> (69)..(96)
<223> nucleótido 2'-O-Me

<220>
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<222> (97)..(100)
<223> Enlace PS, nucleótido 2'-O-Me

<400> 94
uucuuuggca acuuaccag guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguaaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 95
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<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: secuencia modificada de ARNsg G000488 dirigido a TTR humana

<220>
<221> base_modificada
<222> (1)..(3)
<223> Enlace PS, nucleótido 2'-O-Me

<220>
<221> base_modificada
<222> (29)..(40)
<223> nucleótido 2'-O-Me

<220>
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<222> (69)..(96)
<223> nucleótido 2'-O-Me

<220>
<221> base_modificada
<222> (97)..(100)
<223> Enlace PS, nucleótido 2'-O-Me

<400> 95
aaaguucuag augcuguccg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguaaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 96
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<213> Secuencia artificial

<220>
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<221> base_modificada
<222> (1)..(3)
<223> Enlace PS, nucleótido 2'-O-Me

<220>
<221> base_modificada
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<223> nucleótido 2'-O-Me

<220>
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<223> nucleótido 2'-O-Me

<220>
<221> base_modificada
<222> (97)..(100)
<223> Enlace PS, nucleótido 2'-O-Me

<400> 96
uuugaccauc agaggacacu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguaaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 97
<211> 100
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: secuencia modificada de ARNsg G000490 dirigido a TTR humana

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<222> (1)..(3)
<223> Enlace PS, nucleótido 2'-O-Me

<220>
<221> base_modificada
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<223> nucleótido 2'-O-Me

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<223> nucleótido 2'-O-Me

<220>
<221> base_modificada
<222> (97)..(100)
<223> Enlace PS, nucleótido 2'-O-Me

<400> 97
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 98
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<220>
<223> Sintético: secuencia modificada de ARNsg G000491 dirigido a TTR humana

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<223> Enlace PS, nucleótido 2'-O-Me

<220>
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<220>
<221> base_modificada
<222> (69)..(96)
<223> nucleótido 2'-O-Me

<220>
<221> base_modificada
<222> (97)..(100)
<223> Enlace PS, nucleótido 2'-O-Me

<400> 98
auaccagucc agcaaggcag guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 99
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<212> ARN
<213> Secuencia artificial

<220>
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<223> Enlace PS, nucleótido 2'-O-Me

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<223> nucleótido 2'-O-Me

<220>
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<222> (69)..(96)
<223> nucleótido 2'-O-Me

<220>
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<222> (97)..(100)
<223> Enlace PS, nucleótido 2'-O-Me

<400> 99
cuucucuaca cccagggcac guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguaaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 100
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<213> Secuencia artificial

<220>
<223> Sintético: secuencia modificada de ARNsg G000493 dirigido a TTR humana

<220>
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<222> (1)..(3)
<223> Enlace PS, nucleótido 2'-O-Me

<220>
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<220>
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<223> nucleótido 2'-O-Me

<220>
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<222> (97)..(100)
<223> Enlace PS, nucleótido 2'-O-Me

<400> 100
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<222> (1)..(3)
<223> Enlace PS, nucleótido 2'-O-Me

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<223> nucleótido 2'-O-Me

<220>
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<222> (69)..(96)
<223> nucleótido 2'-O-Me

<220>
<221> base_modificada
<222> (97)..(100)
<223> Enlace PS, nucleótido 2'-O-Me

<400> 101
gugagucugg agagcugcau guuuuagagc uagaaaagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 102
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<223> Enlace PS, nucleótido 2'-O-Me

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<222> (69)..(96)
<223> nucleótido 2'-O-Me

<220>
<221> base_modificada
<222> (97)..(100)
<223> Enlace PS, nucleótido 2'-O-Me

<400> 102
cagaggacac uuggauucac guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 103
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<220>
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<223> Enlace PS, nucleótido 2'-O-Me

<220>
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<223> nucleótido 2'-O-Me

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<222> (69)..(96)
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<220>
<221> base_modificada
<222> (97)..(100)
<223> Enlace PS, nucleótido 2'-O-Me

<400> 103
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 104
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<223> Enlace PS, nucleótido 2'-O-Me

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<223> nucleótido 2'-O-Me

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<222> (69)..(96)
<223> nucleótido 2'-O-Me

<220>
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<222> (97)..(100)
<223> Enlace PS, nucleótido 2'-O-Me

<400> 104
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<223> Enlace PS, nucleótido 2'-O-Me

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<222> (29)..(40)
<223> nucleótido 2'-O-Me

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<222> (69)..(96)
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<220>
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<222> (97)..(100)
<223> Enlace PS, nucleótido 2'-O-Me

<400> 105
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cguaaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<223> Enlace PS, nucleótido 2'-O-Me

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<222> (69)..(96)
<223> nucleótido 2'-O-Me

<220>
<221> base_modificada
<222> (97)..(100)
<223> Enlace PS, nucleótido 2'-O-Me

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cguaaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<223> Sintético: secuencia modificada de ARNsg G000500 dirigido a TTR humana

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<222> (1)..(3)
<223> Enlace PS, nucleótido 2'-O-Me

<220>
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<223> nucleótido 2'-O-Me

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<221> base_modificada

<222> (69)..(96)

<223> nucleótido 2'-O-Me

<220>

<221> base_modificada

<222> (97)..(100)

<223> Enlace PS, nucleótido 2'-O-Me

<400> 107

ccaguccagc aaggcagagg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<223> Sintético: secuencia modificada de ARNsg G000501 dirigido a TTR humana

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<222> (1)..(3)

<223> Enlace PS, nucleótido 2'-O-Me

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<222> (29)..(40)

<223> nucleótido 2'-O-Me

<220>

<221> base_modificada

<222> (69)..(96)

<223> nucleótido 2'-O-Me

<220>

<221> base_modificada

<222> (97)..(100)

<223> Enlace PS, nucleótido 2'-O-Me

<400> 108

ucacagaaac acucaccgua guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<212> ARN

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<223> Sintético: secuencia modificada de ARNsg G000567 dirigido a TTR humana

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<223> Enlace PS, nucleótido 2'-O-Me

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<220>
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<222> (69)..(96)
<223> nucleótido 2'-O-Me

<220>
<221> base_modificada
<222> (97)..(100)
<223> Enlace PS, nucleótido 2'-O-Me

<400> 109
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cguaaucaac ugaaaaaagu ggcaccgagu cggugcuuuu 100

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<223> Sintético: secuencia modificada de ARNsg G000568 dirigido a TTR humana

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<223> Enlace PS, nucleótido 2'-O-Me

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<222> (97)..(100)
<223> Enlace PS, nucleótido 2'-O-Me

<400> 110

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cguaaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<223> Sintético: secuencia modificada de ARNsg G000570 dirigido a TTR humana

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<222> (1)..(3)
<223> Enlace PS, nucleótido 2'-O-Me

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<222> (69)..(96)
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<220>
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<222> (97)..(100)
<223> Enlace PS, nucleótido 2'-O-Me

<400> 111
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cguaaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<223> Sintético: secuencia modificada de ARNsg G000571 dirigido a TTR humana

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<223> Enlace PS, nucleótido 2'-O-Me

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<223> Enlace PS, nucleótido 2'-O-Me

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<223> Enlace PS, nucleótido 2'-O-Me

<400> 113
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<223> Enlace PS, nucleótido 2'-O-Me

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<223> Enlace PS, nucleótido 2'-O-Me

<400> 114
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<223> Enlace PS, nucleótido 2'-O-Me

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<223> Enlace PS, nucleótido 2'-O-Me

<400> 115
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<210> 116
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<223> Enlace PS, nucleótido 2'-O-Me

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<223> Enlace PS, nucleótido 2'-O-Me

<400> 116
aaaggcugcu gaugagaccu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

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<223> Enlace PS, nucleótido 2'-O-Me

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<223> Enlace PS, nucleótido 2'-O-Me

<400> 117
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cguaaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<223> Enlace PS, nucleótido 2'-O-Me

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cguaaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<223> Enlace PS, nucleótido 2'-O-Me

<400> 119
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cguaaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<223> Enlace PS, nucleótido 2'-O-Me

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<223> Enlace PS, nucleótido 2'-O-Me

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cguaaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<400> 121
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<223> Enlace PS, nucleótido 2'-O-Me

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<223> nucleótido 2'-O-Me

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<221> base_modificada

<222> (97)..(100)

<223> Enlace PS, nucleótido 2'-O-Me

<400> 124

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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<223> Sintético: secuencia ejemplar después del extremo 3' de la secuencia de guía

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<210> 199

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<210> 200

<400> 200
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<210> 201

<211> 4140

<212> ADN

<213> Secuencia artificial

<220>

<223> Sintético: secuencia de codificación de ADN de Cas9 que usa análogo de timidina de los codones de mínima uridina enumerados en la Tabla 3, con codones de inicio y de parada

<400> 201

atggacaaga agtacagcat cggactggac atcggaacaa acagcgtcgg atgggcagtc	60
atcacagacg aatacaaggt cccgagcaag aagttcaagg tcctgggaaa cacagacaga	120
cacagcatca agaagaacct gatcggagca ctgctgttcg acagcggaga aacagcagaa	180
gcaacaagac tgaagagaac agcaagaaga agatacacia gaagaaagaa cagaatctgc	240
tacctgcagg aaatcttcag caacgaaatg gcaaaggctg acgacagctt cttccacaga	300
ctggaagaaa gcttcttgtt cgaagaagac aagaagcacg aaagacaccc gatcttcgga	360
aacatcgtcg acgaagtcgc ataccacgaa aagtaccgga caatctacca cctgagaaag	420
aagctggtcg acagcacaga caaggcagac ctgagactga tctacctggc actggcacac	480
atgatcaagt tcagaggaca cttctgatc gaaggagacc tgaaccgga caacagcgac	540
gtcgacaagc tgttcatcca gctgttcag acatacaacc agctgttcga agaaaacccg	600
atcaacgcaa gcggagtcca cgcaaaggca atcctgagcg caagactgag caagagcaga	660
agactggaaa acctgatcgc acagctgccg ggagaaaaga agaacggact gttcggaaac	720
ctgatcgcac tgagcctggg actgacaccg aactcaaga gcaacttga cctggcagaa	780
gacgcaaagc tgcagctgag caaggacaca tacgacgacg acctggacaa cctgctggca	840
cagatcggag accagtacgc agacctgttc ctggcagcaa agaacctgag cgacgcaatc	900
ctgctgagcg acatcctgag agtcaacaca gaaatcacia aggcaccgct gagcgcaagc	960
atgatcaaga gatacgacga acaccaccag gacctgacac tgctgaaggc actggtcaga	1020
cagcagctgc cggaaaagta caaggaaatc ttcttcgacc agagcaagaa cggatacgca	1080
ggatacatcg acggaggagc aagccaggaa gaattctaca agttcatcaa gccgatcctg	1140
gaaaagatgg acggaacaga agaactgtct gtcaagctga acagagaaga cctgctgaga	1200
aagcagagaa cattcgacaa cggaagcatc ccgcaccaga tccacctggg agaactgcac	1260
gcaatcctga gaagacagga agacttctac ccgttcctga aggacaacag agaaaagatc	1320

gaaaagatcc tgacattcag aatcccgtag tacgtcggac cgctggcaag aggaaacagc 1380
agattcgcat ggatgacaag aaagagcgaa gaaacaatca caccgtggaa cttcgaagaa 1440
gtcgtcgaca agggagcaag cgcacagagc ttcacgaaa gaatgacaaa cttcgacaag 1500
aacctgccga acgaaaaggt cctgccgaag cacagcctgc tgtacgaata cttcacagtc 1560
tacaacgaac tgacaaaggt caagtacgtc acagaaggaa tgagaaagcc ggcattcctg 1620
agcggagAAC agaagaaggc aatcgtcgac ctgctgttca agacaaacag aaaggtcaca 1680
gtcaagcagc tgaaggaaga ctacttcaag aagatcgaat gcttcgacag cgtcgaaatc 1740
agcggagtcg aagacagatt caacgcaagc ctgggaacat accacgacct gctgaagatc 1800
atcaaggaca aggacttctt ggacaacgaa gaaaacgaag acatcctgga agacatcgtc 1860
ctgacactga cactgttcga agacagagaa atgatcgaag aaagactgaa gacatacgca 1920
cacctgttcg acgacaaggt catgaagcag ctgaagagaa gaagatacac aggatgggga 1980
agactgagca gaaagctgat caacggaatc agagacaagc agagcggaaa gacaatcctg 2040
gacttctga agagcgacgg attcgcaaac agaaacttca tgcagctgat ccacgacgac 2100
agcctgacat tcaaggaaga catccagaag gcacaggtca gcggacaggg agacagcctg 2160
cacgaacaca tcgcaaactt ggacaggaagc ccggcaatca agaagggaat cctgcagaca 2220
gtcaaggtcg tcgacgaact ggtcaaggtc atgggaagac acaagccgga aaacatcgtc 2280
atcgaaatgg caagagaaaa ccagacaaca cagaaggagc agaagaacag cagagaaaga 2340
atgaagagaa tcgaagaagg aatcaaggaa ctgggaagcc agatcctgaa ggaacacccg 2400
gtcgaaaaca cacagctgca gaacgaaaag ctgtacctgt actacctgca gaacggaaga 2460
gacatgtacg tcgaccagga actggacatc aacagactga gcgactacga cgtcgaccac 2520
atcgtccgcg agagcttctt gaaggacgac agcatcgaca acaaggtcct gacaagaagc 2580
gacaagaaca gaggaagagc cgacaacgtc ccgagcgaag aagtcgtcaa gaagatgaag 2640
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acaaaggcag agagaggagg actgagcgaa ctggacaagg caggattcat caagagacag 2760
ctggtcgaaa caagacagat cacaagcac gtcgcacaga tcctggacag cagaatgaac 2820
acaaagtacg acgaaaacga caagctgatc agagaagtca aggtcatcac actgaagagc 2880
aagctggtca gcgacttcag aaaggacttc cagttctaca aggtcagaga aatcaacaac 2940
taccaccagc cacacgacgc atacctgaac gcagtcgtcg gaacagcact gatcaagaag 3000
taccgaagc tggaagcga attcgtctac ggagactaca aggtctacga cgtcagaaag 3060

atgatcgcaa agagcgaaca ggaaatcgga aaggcaacag caaagtactt cttctacagc 3120
aacatcatga acttcttcaa gacagaaatc aactggcaa acggagaaat cagaaagaga 3180
ccgctgatcg aaacaaacgg agaaacagga gaaatcgtct gggacaaggg aagagacttc 3240
gcaacagtca gaaaggtcct gagcatgccg caggtcaaca tcgtcaagaa gacagaagtc 3300
cagacaggag gattcagcaa ggaaagcatc ctgccgaaga gaaacagcga caagctgatc 3360
gcaagaaaga aggactggga cccgaagaag tacggaggat tcgacagccc gacagtcgca 3420
tacagcgtcc tggctgtcgc aaaggtcgaa aagggaaga gcaagaagct gaagagcgtc 3480
aaggaaactgc tgggaatcac aatcatggaa agaagcagct tcgaaaagaa cccgatcgac 3540
ttcctggaag caaagggata caaggaagtc aagaaggacc tgatcatcaa gctgccgaag 3600
tacagcctgt tcgaactgga aaacggaaga aagagaatgc tggcaagcgc aggagaactg 3660
cagaagggaa acgaactggc actgccgagc aagtacgtca acttcctgta cctggcaagc 3720
cactacgaaa agctgaaggg aagcccgaa gacaacgaac agaagcagct gttcgtcgaa 3780
cagcacaagc actacctgga cgaaatcatc gaacagatca gcgaattcag caagagagtc 3840
atcctggcag acgcaaacct ggacaaggtc ctgagcgcac acaacaagca cagagacaag 3900
ccgatcagag aacaggcaga aaacatcatc cacctgttca cactgacaaa cctgggagca 3960
ccggcagcat tcaagtactt cgacacaaca atcgacagaa agagatacac aagcacaag 4020
gaagtcttgg acgcaacact gatccaccag agcatcacag gactgtacga aacaagaatc 4080
gacctgagcc agctgggagg agacggagga ggaagcccga agaagaagag aaaggtctag 4140

<210> 202

<211> 4143

<212> ADN

<213> Secuencia artificial

<220>

<223> Sintético: secuencia de codificación de ADN de Cas9 que usa codones con expresión generalmente alta en humanos

<400> 202

atggataaga agtactcaat cgggctggat atcggaacta attccgtggg ttgggcagtg 60

atcacggatg aatacaaagt gccgtccaag aagtccaagg tcctggggaa caccgataga 120

cacagcatca agaaaaatct catcgagacc ctgctgtttg actccggcga aaccgcagaa 180

gcgacccggc taaacgtac cgcgaggcga cgctacacc ggcggaagaa tcgcatctgc 240

tatctgcaag agatcttttc gaacgaaatg gcaaaggtcg acgacagctt cttccaccgc 300

ctggaagaat ctttctggt ggaggaggac aagaagcatg aacggcatcc tatctttgga 360

aacatcgctg acgaagtggc gtaccacgaa aagtaccca ccatctacca tctgcggaag 420
 aagttggtg actcaactga caaggccgac ctgagattga tctacttggc cctcgcccat 480
 atgatcaaat tccgcgga cttctgatc gaaggcgatc tgaaccctga taactccgac 540
 gtggataagc ttttcattca actggtgcag acctacaacc aactgttcga agaaaaccca 600
 atcaatgcta gcggcgctga tgccaaggcc atcctgtccg cccggctgtc gaagtcgagg 660
 cgctcgaaa acctgatcg acagctgccg ggagagaaaa agaacggact tttcggaac 720
 ttgatcgctc tctactggg actcactccc aattcaagt ccaattttga cctggccgag 780
 gacgcgaagc tgcaactctc aaaggacacc tacgacgacg acttgacaa tttgtggca 840
 caaattggcg atcagtagc ggatctgtt cttgccgcta agaacccttc ggacgcaatc 900
 ttgtgtccg atatcctgcg cgtgaacacc gaaataacca aagcgccgct tagcgctcg 960
 atgattaagc ggtacgacga gcatcaccag gatctcacg tgctcaaagc gctcgtgaga 1020
 cagcaactgc ctgaaaagta caaggagatc ttctcgacc agtccaagaa tgggtacgca 1080
 gggtagatcg atggaggcg tagccaggaa gagttctata agttcatca gccaatcctg 1140
 gaaaagatgg acggaaccga agaactgctg gtcaagctga acaggaggga tctgctccgg 1200
 aaacagagaa ctttgacaa cggatccatt cccaccaga tccatctggg tgagctgcac 1260
 gccatcttc gccgccgga ggactttac ccattctca aggacaaccg ggaaaagatc 1320
 gagaaaattc tgacgttccg catccgtat tacgtgggccc cactggcgcg cggcaattcg 1380
 cgcttcgctg gatgactag aaaatcagag gaaacatca ctccttgga tttcgaggaa 1440
 gttgtggata agggagcttc ggcacaaagc ttcatgaa gaatgacaa cttcgacaag 1500
 aatctccaa acgagaaggt gttcctaag cacagcctcc ttacgaata cttactgtc 1560
 tacaacgaac tgactaaagt gaaatacgtt actgaaggaa tgaggaagcc ggccttctg 1620
 tccggagaac agaagaaagc aattgtgat ctgctgttca agaccaaccg caagtgacc 1680
 gtcaagcagc ttaaagagga ctacttaag aagatcgagt gtttcgactc agtggaatc 1740
 agcggggtg aggacagatt caacgcttcg ctgggaacct atcatgatc cctgaagatc 1800
 atcaaggaca aggacttct tgacaacgag gagaacgagg acatcctgga agatcgtc 1860
 ctgacctga ccctttcga ggatcgcgag atgatcagg agaggctta gacctacgt 1920
 catctcttc acgataaggt catgaaaca ctcaagcgc gccggtacac tggttggggc 1980
 cgctctccc gcaagctgat caacgttatt cgcgataaac agagcggtaa aactatcctg 2040
 gatttctca aatcggtatg cttcgtaat cgtaacttca tgcaattgat ccacgacgac 2100
 agcctgacct ttaaggagga catcaaaaa gcacaagtgt ccggacagg agactcactc 2160

catgaacaca tcgcgaatct ggccggttcg ccggcgatta agaagggaat tctgcaaact 2220
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gtggaaaaca cgacgtgca gaacgagaag ctctacctgt actatttgca aaatggacgg 2460
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taccctaaac ttgaatcgga gtttgttac ggagactaca aggtctacga cgtgaggaag 3060
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aacatcatga actttttcaa gactgaaatt acgctggcca atggagaaat caggaagagg 3180
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gcaactgttc gcaaagtgt ctctatgcc caagtcaata ttgtgaagaa aaccgaagtg 3300
caaaccggcg gattttcaaa ggaatcgatc ctccaaaga gaaatagcga caagtcatt 3360
gcacgcaaga aagactggga cccgaagaag tacggaggat tcgattcgcc gactgtcgca 3420
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ttcctcgagg cgaagggtta caaggagtg aagaaggatc tgatcatcaa actccccaag 3600
tactactgt tcgaactgga aaatggtcgg aagcgcatgc tggcttcggc cggagaactc 3660
caaaaaggaa atgagctggc ctgcctagc aagtacgtca acttcctcta tcttgcttcg 3720
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ccgatcagag aacaggccga gaacattatc cacttggtca ccctgactaa cctgggagcc 3960
ccagccgcct tcaagtactt cgatactact atcgatcgca aaagatacac gtccaccaag 4020
gaagttctgg acgcgaccct gatccaccaa agcatcactg gactctacga aactaggatc 4080
gatctgtcgc agctgggtgg cgatggcggg ggatctccga aaaagaagag aaaggtgtaa 4140
tga 4143

<210> 203
<211> 1379
<212> PRT
<213> Secuencia artificial

<220>
<223> Sintético: secuencia de aminoácidos de Cas9 con una señal de localización nuclear (1xNLS) como los 7 aminoácidos C-terminales

<400> 203

Met Asp Lys Lys Tyr Ser Ile Gly Leu Asp Ile Gly Thr Asn Ser Val
1 5 10 15

Gly Trp Ala Val Ile Thr Asp Glu Tyr Lys Val Pro Ser Lys Lys Phe
20 25 30

Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys Lys Asn Leu Ile
35 40 45

Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu
50 55 60

Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys
65 70 75 80

Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met Ala Lys Val Asp Asp Ser
85 90 95

Phe Phe His Arg Leu Glu Glu Ser Phe Leu Val Glu Glu Asp Lys Lys
100 105 110

His Glu Arg His Pro Ile Phe Gly Asn Ile Val Asp Glu Val Ala Tyr
115 120 125

His Glu Lys Tyr Pro Thr Ile Tyr His Leu Arg Lys Lys Leu Val Asp
130 135 140

Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile Tyr Leu Ala Leu Ala His

145150155160

Met Ile Lys Phe Arg Gly His Phe Leu Ile Glu Gly Asp Leu Asn Pro

165170175

Asp Asn Ser Asp Val Asp Lys Leu Phe Ile Gln Leu Val Gln Thr Tyr

180185190

Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn Ala Ser Gly Val Asp Ala

195200205

Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys Ser Arg Arg Leu Glu Asn

210215220

Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys Asn Gly Leu Phe Gly Asn

225230235240

Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro Asn Phe Lys Ser Asn Phe

245250255

Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu Ser Lys Asp Thr Tyr Asp

260265270

Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile Gly Asp Gln Tyr Ala Asp

275280285

Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp Ala Ile Leu Leu Ser Asp

290295300

Ile Leu Arg Val Asn Thr Glu Ile Thr Lys Ala Pro Leu Ser Ala Ser

305310315320

Met Ile Lys Arg Tyr Asp Glu His His Gln Asp Leu Thr Leu Leu Lys

325330335

Ala Leu Val Arg Gln Gln Leu Pro Glu Lys Tyr Lys Glu Ile Phe Phe

340345350

Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr Ile Asp Gly Gly Ala Ser

355360365

Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro Ile Leu Glu Lys Met Asp

370375380

Gly Thr Glu Glu Leu Leu Val Lys Leu Asn Arg Glu Asp Leu Leu Arg
385 390 395 400

Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile Pro His Gln Ile His Leu
 405 410 415

Gly Glu Leu His Ala Ile Leu Arg Arg Gln Glu Asp Phe Tyr Pro Phe
 420 425 430

Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile
 435 440 445

Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp
 450 455 460

Met Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu
465 470 475 480

Val Val Asp Lys Gly Ala Ser Ala Gln Ser Phe Ile Glu Arg Met Thr
 485 490 495

Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys Val Leu Pro Lys His Ser
 500 505 510

Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu Leu Thr Lys Val Lys
 515 520 525

Tyr Val Thr Glu Gly Met Arg Lys Pro Ala Phe Leu Ser Gly Glu Gln
 530 535 540

Lys Lys Ala Ile Val Asp Leu Leu Phe Lys Thr Asn Arg Lys Val Thr
545 550 555 560

Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp
 565 570 575

Ser Val Glu Ile Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu Gly
 580 585 590

Thr Tyr His Asp Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp
 595 600 605

Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile Val Leu Thr Leu Thr
 610 615 620

Leu Phe Glu Asp Arg Glu Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala
625 630 635 640

His Leu Phe Asp Asp Lys Val Met Lys Gln Leu Lys Arg Arg Arg Tyr
 645 650 655

Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp
 660 665 670

Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe
 675 680 685

Ala Asn Arg Asn Phe Met Gln Leu Ile His Asp Asp Ser Leu Thr Phe
 690 695 700

Lys Glu Asp Ile Gln Lys Ala Gln Val Ser Gly Gln Gly Asp Ser Leu
705 710 715 720

His Glu His Ile Ala Asn Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly
 725 730 735

Ile Leu Gln Thr Val Lys Val Val Asp Glu Leu Val Lys Val Met Gly
 740 745 750

Arg His Lys Pro Glu Asn Ile Val Ile Glu Met Ala Arg Glu Asn Gln
 755 760 765

Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu Arg Met Lys Arg Ile
 770 775 780

Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile Leu Lys Glu His Pro
785 790 795 800

Val Glu Asn Thr Gln Leu Gln Asn Glu Lys Leu Tyr Leu Tyr Tyr Leu
 805 810 815

Gln Asn Gly Arg Asp Met Tyr Val Asp Gln Glu Leu Asp Ile Asn Arg
 820 825 830

Leu Ser Asp Tyr Asp Val Asp His Ile Val Pro Gln Ser Phe Leu Lys
 835 840 845

Asp Asp Ser Ile Asp Asn Lys Val Leu Thr Arg Ser Asp Lys Asn Arg
 850 855 860

Gly Lys Ser Asp Asn Val Pro Ser Glu Glu Val Val Lys Lys Met Lys
865 870 875 880

Asn Tyr Trp Arg Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys
 885 890 895

Phe Asp Asn Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp
 900 905 910

Lys Ala Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr
 915 920 925

Lys His Val Ala Gln Ile Leu Asp Ser Arg Met Asn Thr Lys Tyr Asp
 930 935 940

Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys Ser
945 950 955 960

Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys Val Arg
 965 970 975

Glu Ile Asn Asn Tyr His His Ala His Asp Ala Tyr Leu Asn Ala Val
 980 985 990

Val Gly Thr Ala Leu Ile Lys Lys Tyr Pro Lys Leu Glu Ser Glu Phe
 995 1000 1005

Val Tyr Gly Asp Tyr Lys Val Tyr Asp Val Arg Lys Met Ile Ala
1010 1015 1020

Lys Ser Glu Gln Glu Ile Gly Lys Ala Thr Ala Lys Tyr Phe Phe
1025 1030 1035

Tyr Ser Asn Ile Met Asn Phe Phe Lys Thr Glu Ile Thr Leu Ala
1040 1045 1050

Asn Gly Glu Ile Arg Lys Arg Pro Leu Ile Glu Thr Asn Gly Glu
1055 1060 1065

Thr Gly Glu Ile Val Trp Asp Lys Gly Arg Asp Phe Ala Thr Val
1070 1075 1080

Arg Lys Val Leu Ser Met Pro Gln Val Asn Ile Val Lys Lys Thr

1085	1090	1095
Glu Val	Gln Thr Gly Gly Phe	Ser Lys Glu Ser Ile Leu Pro Lys
1100	1105	1110
Arg Asn	Ser Asp Lys Leu Ile	Ala Arg Lys Lys Asp Trp Asp Pro
1115	1120	1125
Lys Lys	Tyr Gly Gly Phe Asp	Ser Pro Thr Val Ala Tyr Ser Val
1130	1135	1140
Leu Val	Val Ala Lys Val Glu	Lys Gly Lys Ser Lys Lys Leu Lys
1145	1150	1155
Ser Val	Lys Glu Leu Leu Gly	Ile Thr Ile Met Glu Arg Ser Ser
1160	1165	1170
Phe Glu	Lys Asn Pro Ile Asp	Phe Leu Glu Ala Lys Gly Tyr Lys
1175	1180	1185
Glu Val	Lys Lys Asp Leu Ile	Ile Lys Leu Pro Lys Tyr Ser Leu
1190	1195	1200
Phe Glu	Leu Glu Asn Gly Arg	Lys Arg Met Leu Ala Ser Ala Gly
1205	1210	1215
Glu Leu	Gln Lys Gly Asn Glu	Leu Ala Leu Pro Ser Lys Tyr Val
1220	1225	1230
Asn Phe	Leu Tyr Leu Ala Ser	His Tyr Glu Lys Leu Lys Gly Ser
1235	1240	1245
Pro Glu	Asp Asn Glu Gln Lys	Gln Leu Phe Val Glu Gln His Lys
1250	1255	1260
His Tyr	Leu Asp Glu Ile Ile	Glu Gln Ile Ser Glu Phe Ser Lys
1265	1270	1275
Arg Val	Ile Leu Ala Asp Ala	Asn Leu Asp Lys Val Leu Ser Ala
1280	1285	1290
Tyr Asn	Lys His Arg Asp Lys	Pro Ile Arg Glu Gln Ala Glu Asn
1295	1300	1305

Ile Ile His Leu Phe Thr Leu Thr Asn Leu Gly Ala Pro Ala Ala
1310 1315 1320

Phe Lys Tyr Phe Asp Thr Thr Ile Asp Arg Lys Arg Tyr Thr Ser
1325 1330 1335

Thr Lys Glu Val Leu Asp Ala Thr Leu Ile His Gln Ser Ile Thr
1340 1345 1350

Gly Leu Tyr Glu Thr Arg Ile Asp Leu Ser Gln Leu Gly Gly Asp
1355 1360 1365

Gly Gly Gly Ser Pro Lys Lys Lys Arg Lys Val
1370 1375

<210> 204
<211> 4140
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: ORF del ARNm de Cas9 que usa codones de mínima uridina, con codones de inicio y parada

<400> 204
auggacaaga aguacagcau cggacuggac aucggaacaa acagcgucgg augggcaguc 60
aucacagacg aaucacaaggu cccgagcaag aaguucaagg uccugggaaa cacagacaga 120
cacagcauca agaagaaccu gaucggagca cugcuguucg acagcggaga aacagcagaa 180
gcaacaagac ugaagagaac agcaagaaga agauacacaa gaagaaagaa cagaaucugc 240
uaccugcagg aaauucuucag caacgaaaug gcaaaggucg acgacagcuu cuuccacaga 300
cuggaagaaa gcuuccuggu cgaagaagac aagaagcacg aaagacacc gaucuucgga 360
aacaucgucg acgaagucgc auaccacgaa aaguacccga caaucuacca ccugagaaaag 420
aagcuggucg acagcacaga caaggcagac cugagacuga ucuaccuggc acuggcacac 480
augaucaagu ucagaggaca cuuccugauc gaaggagacc ugaacccgga caacagcgac 540
gucgacaagc uguucaucca gcugguccag acauacaacc agcuguucga agaaaacccg 600
aucaacgcaa gcggagucga cgcaaaggca auccugagcg caagacugag caagagcaga 660
agacuggaaa accugaucgc acagcugccg ggagaaaaga agaacggacu guucggaaac 720
cugaucgcac ugagccuggg acugacaccg aacuucaaga gcaacuucga ccuggcagaa 780
gacgcaaagc ugcagcugag caaggacaca uacgacgacg accuggacaa ccugcuggca 840
cagaucggag accaguacgc agaccuguuc cuggcagcaa agaaccugag cgacgcaauc 900

cugcugagcg acauccugag agucaacaca gaaaucacaa aggcaccgcu gagcgcaagc	960
augaucaaga gauacgacga acaccaccag gaccugacac ugcugaaggc acuggucaga	1020
cagcagcugc cggaaaagua caaggaaauc uucuucgacc agagcaagaa cggauacgca	1080
ggauacaucg acggaggagc aagccaggaa gaauucuaca aguucauaa gccgauccug	1140
gaaaagaugg acggaacaga agaacugcug gucaagcuga acagagaaga ccugcugaga	1200
aagcagagaa cauucgacaa cggaagcauc ccgcaccaga uccaccuggg agaacugcac	1260
gcaauccuga gaagacagga agacuucuac ccguuccuga aggacaacag agaaaagauc	1320
gaaaagaucc ugacauucag aaucccguac uacgucggac cgcuggcaag aggaaacagc	1380
agauucgau ggauagacaag aaagagcgaa gaaacaauc caccugggaa cuucgaagaa	1440
gucgucgaca agggagcaag cgcacagagc uucaucgaaa gaaugacaaa cuucgacaag	1500
aaccugccga acgaaaaggu ccugccgaag cacagccugc uguacgaaua cuucacaguc	1560
uacaacgaac ugacaaaggu caaguacguc acagaaggaa ugagaaagcc ggcauuccug	1620
agcggagaac agaagaaggc aaucgucgac cugcuguuca agacaaacag aaaggucaca	1680
gucaagcagc ugaaggaaga cuacuucaag aagaucgaau gcuucgacag cgucgaaauc	1740
agcggagucg aagacagauu caacgcaagc cugggaacau accacgaccu gcugaagauc	1800
aucaaggaca aggacuuccu ggacaacgaa gaaaacgaag acauccugga agacaucguc	1860
cugacacuga cacuguucga agacagagaa augaucgaag aaagacugaa gacauacgca	1920
caccuguucg acgacaaggu caugaagcag cugaagagaa gaagauacac aggaugggga	1980
agacugagca gaaagcugau caacggaauc agagacaagc agagcggaaa gacaauccug	2040
gacuuccuga agagcgacgg auucgcaaac agaaacuua ugcagcugau ccacgacgac	2100
agccugacau ucaaggaaga cauccagaag gcacagguca gcggacaggg agacagccug	2160
cacgaacaca ucgcaaaccu ggcaaggagc ccggcaauca agaagggaau ccugcagaca	2220
gucaaggucg ugcacgaacu ggucaagguc augggaagac acaagccgga aaacaucguc	2280
aucgaaaugg caagagaaaa ccagacaaca cagaagggac agaagaacag cagagaaaga	2340
augaagagaa ucgaagaagg aaucaggaa cugggaagcc agauccugaa ggaacaccg	2400
gucgaaaaca cacagcugca gaacgaaaag cuguaccugu acuaccugca gaacggaaga	2460
gacauguacg ugcaccagga acuggacauc aacagacuga gcgacuacga cgucgaccac	2520
aucguccgc agagcuuccu gaaggacgac agcaucgaca acaagguccu gacaagaagc	2580
gacaagaaca gaggaagag cgacaacguc ccgagcgaag aagucgucaa gaagaugaag	2640

aacuacugga gacagcugcu gaacgcaaag cugaucacac agagaaaguu cgacaaccug 2700
acaaaggcag agagaggagg acugagcgaa cuggacaagg caggauucau caagagacag 2760
cuggucgaaa caagacagau cacaagcac gucgcacaga uccuggacag cagaaugaac 2820
acaaaguacg acgaaaacga caagcugauc agagaaguca aggucaucac acugaagagc 2880
aagcugguca gcgacuucag aaaggacuuc caguucuaca aggucaagaga aaucacaac 2940
uaccaccacg cacacgacgc auaccugaac gcagucgucg gaacagcacu gaucaagaag 3000
uaccgaagc uggaaagcga auucgucuac ggagacuaca agguacuaga cgucagaaag 3060
augaucgcaa agagcgaaac ggaaucgga aaggcaacag caaguacuu cuucuacagc 3120
aacaucauga acuucuuaa gacagaaauc acacuggcaa acggagaaau cagaaagaga 3180
ccgcugaucg aaacaaacgg agaaacagga gaaucgucu gggacaaggg aagagacuuc 3240
gcaacaguca gaaagguccu gagcaugccg caggucaaca ucgucaagaa gacagaaguc 3300
cagacaggag gauucagcaa ggaaagcauc cugccgaaga gaaacagcga caagcugauc 3360
gcaagaaaga aggacuggga cccgaagaag uacggaggau ucgacagccc gacagucgca 3420
uacagcgucc uggucgucg aaaggucgaa aagggaaga gcaagaagcu gaagagcguc 3480
aaggaacugc ugggaaucaac aaucaggaa agaagcagcu ucgaaaagaa cccgaucgac 3540
uuccuggaag caaagggauc caaggaaguc aagaaggacc ugaucauca gcuccgaag 3600
uacagccugu ucgaacugga aaacggaaga aagagaauugc uggcaagcgaggaggaaacug 3660
cagaagggaac gaacacuggc acugccgagc aaguacguca acuuccugua ccuggcaagc 3720
cacuacgaaa agcugaaggg aagcccgga gacaacgaac agaagcagcu guucgucgaa 3780
cagcacaagc acuaccugga cgaaucauc gaacagauca gcgaauucag caagagaguc 3840
auccuggcag acgcaaaccu ggacaagguc cugagcgcau acaacaagca cagagacaag 3900
ccgaucagag aacaggcaga aaacaucauc caccuguuca cacugacaaa ccugggagca 3960
ccggcagcau ucaaguacuu cgacacaaca aucgacagaa agagauacac aagcacaag 4020
gaaguccugg acgcaacacu gauccaccag agcaucacag gacuguacga aacaagaau 4080
gaccugagcc agcugggagg agacggagga ggaagcccga agaagaagag aaaggucuag 4140

<210> 205

<211> 4143

<212> ARN

<213> Secuencia artificial

<220>

<223> Sintético: ORF del ARNm de Cas9 que usa codones con expresión generalmente alta en humanos, con codones de inicio y parada

<400> 205

auggauaaga aguacucaau cgggcuggau aucggaacua auuccguggg uugggcagug	60
aucacggaug aaauacaaagu gccguccaag aaguucaagg uccuggggaa caccgauaga	120
cacagcauca agaaaaau cuucggagcc cugcuguuug acuccggcga aaccgcagaa	180
gcgacccggc ucaaacguac cgcgaggcga cgcuaacccc ggcggaagaa ucgcaucugc	240
uauugcaag agauuuuuu gaacgaaug gcaaaggucg acgacagcuu cuuccaccgc	300
cuggaagaau cuuuccuggu ggaggaggac aagaagcaug aacggcaucc uauuuugga	360
aacaucgucg acgaaguggc guaccacgaa aaguaccca ccaucuacca ucugcggaag	420
aaguugguug acucaacuga caaggccgac cucagauuga ucuacuuggc ccucgccau	480
augaucaau uccgcggaca cuuccgauc gaaggcgau ugaaccuga uauuccgac	540
guggauaagc uuuucauua acuggugcag accuacaacc aacuguucga agaaaacca	600
aucaaugcua gcggcgucga ugccaaggcc auccuguccg cccggcuguc gaagucgagg	660
cgccugaaa accugaucgc acagcugccg ggagagaaaa agaaccgacu uuucggcaac	720
uugaucguc ucucacuggg acucacuccc aaauucaagu ccauuuuga ccuggccgag	780
gacgcgaagc ugcaacucuc aaaggacacc uacgacgacg acuuggaca uuugcuggca	840
caauuuggcg aucaguacgc ggaucuguuc cuugccgcu agaaccuuuc ggacgcauc	900
uugcuguccg auauccugcg cgugaacacc gaaauacca aagcgccgcu uagcgccug	960
augauuaagc gguacgacga gcauccagc gaucucacgc ugcuaaagc gcucgugaga	1020
cagcaucugc cugaaaagua caaggagau uucuugacc aguccaaga uggguacgca	1080
ggguacaucg auggaggcgc uagccaggaa gaguucuua aguucauca gccauuccg	1140
gaaaagaugg acggaaccga agaacugcug gucaagcuga acaggaggga ucugcuccgg	1200
aaacagagaa ccuuugacaa cggauccauu cccaccaga uccaucuggg ugagcugcac	1260
gccauucugc ggcgccagga ggacuuuuac ccauuccuag aggacaaccg ggaaaagau	1320
gagaaaauuc ugacguuccg cauccguau uacgugggcc cacuggcgcg cggcaauucg	1380
cgcucgcgu ggaugacuag aaaaucagag gaaaccaua cuccuuggaa uuucgaggaa	1440
guuguggaua agggagcuuc ggcacaaagc uucaucgaac gaaugacca cuucgacaag	1500
aaucuccaa acgagaaggu gcuuccuaag cacagccucc uuacgaaua cuucacuguc	1560
uacaacgaac ugacuaaagu gaaauacguu acugaaggaa ugaggaagcc ggccuuucg	1620
uccggagaac agaagaaagc aaugucgau cugcuguuca agaccaaccg caaggugacc	1680
gucaagcagc uuaaagagga cuacuuaag aagaucgagu guuucgacuc aguggaauc	1740

agcggggugg aggacagauu caacgcuucg cugggaaccu aucaugaucu ccugaagauc 1800
 aucaaggaca aggacuuccu ugacaacgag gagaacgagg acauccugga agauaucguc 1860
 cugaccuuga cccuuuucga ggaucgcgag augaucgagg agaggcuuaa gaccuacgcu 1920
 caucucuucg acgauaaggu caugaaacaa cucaagcgcc gccgguacac ugguuggggc 1980
 cgccucuccc gcaagcugau caacgguaau cgcgauaaac agagcgguaa aacuauccug 2040
 gauuuccuca aaucggauagg cuucgcuaau cguaacuua ugcaauugau ccacgacgac 2100
 agccugaccu uuaaggagga cauccaaaaa gcacaagugu ccggacaggg agacucacuc 2160
 caugaacaca ucgcgaaucg ggccggguucg ccggcgauua agaagggaau ucugcaaacu 2220
 gugaaggugg ucgacgagcu ggugaagguc augggacggc acaaaccgga gaauaucgug 2280
 auugaaaugg cccgagaaaa ccagacuacc cagaagggcc agaaaaacuc ccgcgaaagg 2340
 augaagcgga ucgaagaagg aaucaggag cugggcagcc agauccugaa agagcacccg 2400
 guggaaaaca cgcagcugca gaacgagaag cucuaccugu acuauuugca aaauggacgg 2460
 gacauguacg uggaccaaga gcuggacauc aaucgguuugu cugauuacga cguggaccac 2520
 aucguuccac aguccuuucu gaaggauagc ucgaucgaua acaagguguu gacucgcagc 2580
 gacaagaaca gagggaaguc agauaaugug ccaucggagg agguugugaa gaagaugaag 2640
 aaauacuggc ggcagcuccu gaaugcgaag cugauuaccc agagaaaguu ugacaauuc 2700
 acuaaagccg agcgcggcgg acucucagag cuggauaagg cuggauucau caaacggcag 2760
 cuggucgaga cugggcagau uaccaagcac guggcgaga ucuuggacuc ccgcaugaac 2820
 acuaaaucg acgagaacga uaagcucauc cgggaaguga agguugauuac ccugaaaagc 2880
 aaacuugugu cggacuucg gaaggacuuu caguuuuaca aagugagaga aaucacaac 2940
 uaccaucacg cgcaugacgc auaccucaac gcuguggucg guaccgccc gaucaaaaag 3000
 uaccuaaac uugaaucgga guuuguguac ggagacuaca aggucuacga cgugaggaag 3060
 augauagcca aguccgaaca ggaaucggg aaagcaacug cgaaauacuu cuuuuacuca 3120
 aacauauga acuuuuucaa gacugaaau acgcuggcca auggagaaau caggaagagg 3180
 ccacugaucg aaacuaacgg agaaacgggc gaaucgugu gggacaaggg cagggacuuc 3240
 gcaacuguuc gcaaagugcu cucuaugccg caagucaaua uugugaagaa aaccgaagug 3300
 caaacggcg gauuuucaa ggaucgauc cucccaaaga gaaauagcga caagcucau 3360
 gcacgcaaga aagacuggga cccgaagaag uacggaggau ucgauucgcc gacugucgca 3420
 uacuccgucc ucguugggc caagguggag aagggaaga gcaaaaagcu caaauccguc 3480

aaagagcugc ugagggauuac caucauggaa cgauccucgu ucgagaagaa cccgauugau 3540
uuccucgagg cgaaggguua caaggaggug aagaaggau ugaucacaa acuccccaag 3600
uacucacugu ucgaacugga aaauggucgg aagcgcaugc ugguucggc cggagaacuc 3660
caaaaaggaa augagcuggc cuugccuagc aaguacguca acuuccucua ucuugcuucg 3720
cacuacgaaa aacucaaagg gucaccgga gaauacgaac agaagcagcu uuucguggag 3780
cagcacaagc auuauucugga ugaaauauc gaacaauc ccgaguuuuc aaagcgug 3840
auccucgccg acgccaaccu cgacaaagc cugucggccu acauaagca uagagauaag 3900
ccgaucagag aacaggccga gaacauuau cacuuguuca ccugggagcc 3960
ccagccgccu ucaaguacuu cgauacuacu aucgaucgca aaagauacac guccaccaag 4020
gaaguucugg acgcgacccu gauccacaa agcaucacug gacucucga aacuaggau 4080
gaucugucgc agcugggugg cgauggcggu ggaucuccga aaaagaagag aaagguguaa 4140

uga 4143

<210> 206
<211> 1379
<212> PRT
<213> Secuencia artificial

<220>
<223> Sintético: secuencia de aminoácidos de la nickasa Cas9 (D10A)

<400> 206

Met Asp Lys Lys Tyr Ser Ile Gly Leu Ala Ile Gly Thr Asn Ser Val
1 5 10 15

Gly Trp Ala Val Ile Thr Asp Glu Tyr Lys Val Pro Ser Lys Lys Phe
20 25 30

Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys Lys Asn Leu Ile
35 40 45

Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu
50 55 60

Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys
65 70 75 80

Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met Ala Lys Val Asp Asp Ser
85 90 95

Phe Phe His Arg Leu Glu Glu Ser Phe Leu Val Glu Glu Asp Lys Lys
100 105 110

His Glu Arg His Pro Ile Phe Gly Asn Ile Val Asp Glu Val Ala Tyr
115 120 125

His Glu Lys Tyr Pro Thr Ile Tyr His Leu Arg Lys Lys Leu Val Asp
130 135 140

Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile Tyr Leu Ala Leu Ala His
145 150 155 160

Met Ile Lys Phe Arg Gly His Phe Leu Ile Glu Gly Asp Leu Asn Pro
165 170 175

Asp Asn Ser Asp Val Asp Lys Leu Phe Ile Gln Leu Val Gln Thr Tyr
180 185 190

Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn Ala Ser Gly Val Asp Ala
195 200 205

Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys Ser Arg Arg Leu Glu Asn
210 215 220

Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys Asn Gly Leu Phe Gly Asn
225 230 235 240

Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro Asn Phe Lys Ser Asn Phe
245 250 255

Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu Ser Lys Asp Thr Tyr Asp
260 265 270

Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile Gly Asp Gln Tyr Ala Asp
275 280 285

Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp Ala Ile Leu Leu Ser Asp
290 295 300

Ile Leu Arg Val Asn Thr Glu Ile Thr Lys Ala Pro Leu Ser Ala Ser
305 310 315 320

Met Ile Lys Arg Tyr Asp Glu His His Gln Asp Leu Thr Leu Leu Lys
325 330 335

Ala Leu Val Arg Gln Gln Leu Pro Glu Lys Tyr Lys Glu Ile Phe Phe
340 345 350

Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr Ile Asp Gly Gly Ala Ser
355 360 365

Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro Ile Leu Glu Lys Met Asp
370 375 380

Gly Thr Glu Glu Leu Leu Val Lys Leu Asn Arg Glu Asp Leu Leu Arg
385 390 395 400

Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile Pro His Gln Ile His Leu
405 410 415

Gly Glu Leu His Ala Ile Leu Arg Arg Gln Glu Asp Phe Tyr Pro Phe
420 425 430

Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile
435 440 445

Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp
450 455 460

Met Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu
465 470 475 480

Val Val Asp Lys Gly Ala Ser Ala Gln Ser Phe Ile Glu Arg Met Thr
485 490 495

Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys Val Leu Pro Lys His Ser
500 505 510

Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu Leu Thr Lys Val Lys
515 520 525

Tyr Val Thr Glu Gly Met Arg Lys Pro Ala Phe Leu Ser Gly Glu Gln
530 535 540

Lys Lys Ala Ile Val Asp Leu Leu Phe Lys Thr Asn Arg Lys Val Thr
545 550 555 560

Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp
565 570 575

Ser Val Glu Ile Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu Gly
580 585 590

Thr Tyr His Asp Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp
595 600 605

Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile Val Leu Thr Leu Thr
610 615 620

Leu Phe Glu Asp Arg Glu Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala
625 630 635 640

His Leu Phe Asp Asp Lys Val Met Lys Gln Leu Lys Arg Arg Arg Tyr
645 650 655

Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp
660 665 670

Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe
675 680 685

Ala Asn Arg Asn Phe Met Gln Leu Ile His Asp Asp Ser Leu Thr Phe
690 695 700

Lys Glu Asp Ile Gln Lys Ala Gln Val Ser Gly Gln Gly Asp Ser Leu
705 710 715 720

His Glu His Ile Ala Asn Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly
725 730 735

Ile Leu Gln Thr Val Lys Val Val Asp Glu Leu Val Lys Val Met Gly
740 745 750

Arg His Lys Pro Glu Asn Ile Val Ile Glu Met Ala Arg Glu Asn Gln
755 760 765

Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu Arg Met Lys Arg Ile
770 775 780

Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile Leu Lys Glu His Pro
785 790 795 800

Val Glu Asn Thr Gln Leu Gln Asn Glu Lys Leu Tyr Leu Tyr Tyr Leu

805	810	815
Gln Asn Gly Arg Asp Met Tyr Val Asp Gln Glu Leu Asp Ile Asn Arg		
820	825	830
Leu Ser Asp Tyr Asp Val Asp His Ile Val Pro Gln Ser Phe Leu Lys		
835	840	845
Asp Asp Ser Ile Asp Asn Lys Val Leu Thr Arg Ser Asp Lys Asn Arg		
850	855	860
Gly Lys Ser Asp Asn Val Pro Ser Glu Glu Val Val Lys Lys Met Lys		
865	870	875
Asn Tyr Trp Arg Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys		
885	890	895
Phe Asp Asn Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp		
900	905	910
Lys Ala Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr		
915	920	925
Lys His Val Ala Gln Ile Leu Asp Ser Arg Met Asn Thr Lys Tyr Asp		
930	935	940
Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys Ser		
945	950	955
Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys Val Arg		
965	970	975
Glu Ile Asn Asn Tyr His His Ala His Asp Ala Tyr Leu Asn Ala Val		
980	985	990
Val Gly Thr Ala Leu Ile Lys Lys Tyr Pro Lys Leu Glu Ser Glu Phe		
995	1000	1005
Val Tyr Gly Asp Tyr Lys Val Tyr Asp Val Arg Lys Met Ile Ala		
1010	1015	1020
Lys Ser Glu Gln Glu Ile Gly Lys Ala Thr Ala Lys Tyr Phe Phe		
1025	1030	1035

Tyr Ser Asn Ile Met Asn Phe Phe Lys Thr Glu Ile Thr Leu Ala
1040 1045 1050

Asn Gly Glu Ile Arg Lys Arg Pro Leu Ile Glu Thr Asn Gly Glu
1055 1060 1065

Thr Gly Glu Ile Val Trp Asp Lys Gly Arg Asp Phe Ala Thr Val
1070 1075 1080

Arg Lys Val Leu Ser Met Pro Gln Val Asn Ile Val Lys Lys Thr
1085 1090 1095

Glu Val Gln Thr Gly Gly Phe Ser Lys Glu Ser Ile Leu Pro Lys
1100 1105 1110

Arg Asn Ser Asp Lys Leu Ile Ala Arg Lys Lys Asp Trp Asp Pro
1115 1120 1125

Lys Lys Tyr Gly Gly Phe Asp Ser Pro Thr Val Ala Tyr Ser Val
1130 1135 1140

Leu Val Val Ala Lys Val Glu Lys Gly Lys Ser Lys Lys Leu Lys
1145 1150 1155

Ser Val Lys Glu Leu Leu Gly Ile Thr Ile Met Glu Arg Ser Ser
1160 1165 1170

Phe Glu Lys Asn Pro Ile Asp Phe Leu Glu Ala Lys Gly Tyr Lys
1175 1180 1185

Glu Val Lys Lys Asp Leu Ile Ile Lys Leu Pro Lys Tyr Ser Leu
1190 1195 1200

Phe Glu Leu Glu Asn Gly Arg Lys Arg Met Leu Ala Ser Ala Gly
1205 1210 1215

Glu Leu Gln Lys Gly Asn Glu Leu Ala Leu Pro Ser Lys Tyr Val
1220 1225 1230

Asn Phe Leu Tyr Leu Ala Ser His Tyr Glu Lys Leu Lys Gly Ser
1235 1240 1245

Pro Glu Asp Asn Glu Gln Lys Gln Leu Phe Val Glu Gln His Lys
1250 1255 1260

His Tyr Leu Asp Glu Ile Ile Glu Gln Ile Ser Glu Phe Ser Lys
1265 1270 1275

Arg Val Ile Leu Ala Asp Ala Asn Leu Asp Lys Val Leu Ser Ala
1280 1285 1290

Tyr Asn Lys His Arg Asp Lys Pro Ile Arg Glu Gln Ala Glu Asn
1295 1300 1305

Ile Ile His Leu Phe Thr Leu Thr Asn Leu Gly Ala Pro Ala Ala
1310 1315 1320

Phe Lys Tyr Phe Asp Thr Thr Ile Asp Arg Lys Arg Tyr Thr Ser
1325 1330 1335

Thr Lys Glu Val Leu Asp Ala Thr Leu Ile His Gln Ser Ile Thr
1340 1345 1350

Gly Leu Tyr Glu Thr Arg Ile Asp Leu Ser Gln Leu Gly Gly Asp
1355 1360 1365

Gly Gly Gly Ser Pro Lys Lys Lys Arg Lys Val
1370 1375

<210> 207
<211> 4140
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: ORF del ARNm de la nickasa Cas9 (D10A)

<400> 207
auggacaaga aguacagcau cggacuggca aucggaacaa acagcgucgg augggcaguc 60
aucacagacg aaaucaaggu cccgagcaag aaguucaagg uccugggaaa cacagacaga 120
cacagcauca agaagaaccu gaucggagca cugcuguucg acagcggaga aacagcagaa 180
gcaacaagac ugaagagaac agcaagaaga agauacacaa gaagaaagaa cagaaucugc 240
uaccugcagg aaaucuucag caacgaaaug gcaaaggucg acgacagcuu cuuccacaga 300
cuggaagaaa gcuuccuggu cgaagaagac aagaagcacg aaagacaccc gaucuucgga 360
aauaucgucg acgaagucgc auaccacgaa aaguacccga caaucuacca ccugagaaaag 420
aagcuggucg acagcacaga caaggcagac cugagacuga ucuaccuggc acuggcacac 480
augaucaagu ucagaggaca cuuccugauc gaaggagacc ugaacccgga caacagcgac 540

gucgacaagc uguucaucca gcugguccag acauacaacc agcuguucga agaaaacccg	600
aucaacgcaa gcggagucga cgcaaaggca auccugagcg caagacugag caagagcaga	660
agacuggaaa accugaucgc acagcugccg ggagaaaaga agaacggacu guucggaaac	720
cugaucgcac ugagccuggg acugacaccg aacuuaaga gcaacuucga ccuggcagaa	780
gacgcaaagc ugcagcugag caaggacaca uacgacgacg accuggacaa ccugcuggca	840
cagaucggag accaguacgc agaccuguuc cuggcagcaa agaaccugag cgacgcaauc	900
cugcugagcg acauccugag agucaacaca gaaaucaaa aggcaccgcu gagcgcaagc	960
augaucaaga gauacgacga acaccaccag gaccugacac ugcugaaggc acuggucaga	1020
cagcagcugc cggaaaagua caaggaaauc uucuucgacc agagcaagaa cggauacgca	1080
ggauacaucg acggaggagc aagccaggaa gaauucuaca aguucauaa gccgauccug	1140
gaaaagaugg acggaacaga agaacugcug gucaagcuga acagagaaga ccugcugaga	1200
aagcagagaa cauucgacaa cggaagcauc ccgcaccaga uccaccuggg agaacugcac	1260
gcaauccuga gaagacagga agacuucuac ccguuccuga aggacaacag agaaaagauc	1320
gaaaagaucc ugacauucag aaucccgua uacgucggac cgcuggcaag aggaaacagc	1380
agauucgcau ggauagacaag aaagagcgaa gaaacaauc caccugggaa cuucgaagaa	1440
gucgucgaca agggagcaag cgcacagagc uucaucgaaa gaaugacaaa cuucgacaag	1500
aaccugccga acgaaaaggu ccugccgaag cacagccugc uguacgaaua cuucacaguc	1560
uacaacgaac ugacaaaggu caaguacguc acagaaggaa ugagaaagcc ggcauuccug	1620
agcggagaac agaagaaggc aaucgucgac cugcuguuca agacaaacag aaaggucaca	1680
gucaagcagc ugaaggaaga cuacuuaag aagaucgaau gcuucgacag cgucgaaauc	1740
agcggagucg aagacagauu caacgcaagc cugggaacau accacgaccu gcugaagauc	1800
aucaaggaca aggacuuccu ggacaacgaa gaaaacgaag acauccugga agacaucguc	1860
cugacacuga cacuguucga agacagagaa augaucgaag aaagacugaa gacauacgca	1920
caccuguucg acgacaaggu caugaagcag cugaagagaa gaagauacac aggaugggga	1980
agacugagca gaaagcugau caacggaauc agagacaagc agagcggaaa gacaauccug	2040
gacuuccuga agagcgacgg auucgcaaac agaaacuua ugcagcugau ccacgacgac	2100
agccugacau ucaaggaaga cauccagaag gcacagguca gcggacaggg agacagccug	2160
cacgaacaca ucgcaaaccu ggcaaggaag ccggcaauca agaagggaau ccugcagaca	2220
gucaaggucg ugcacgaacu gguaagguc augggaagac acaagccgga aaacaucguc	2280

aucgaaaugg caagagaaaa ccagacaaca cagaagggac agaagaacag cagagaaaga	2340
augaagagaa ucgaagaagg aaUCAaggaa cugggaagcc agaUccugaa ggaacacccg	2400
gucgaaaaca cacagcugca gaacgaaaag cuguaccugu acuaccugca gaacggaaga	2460
gacauguacg ucgaccagga acuggacauc aacagacuga gcgacuacga cgucgaccac	2520
aucgucccg agagcuuccu gaaggacgac agcaucgaca acaagguccu gacaagaagc	2580
gacaagaaca gaggaagag cgacaacguc ccgagcgaag aagucgucaa gaagaugaag	2640
aacuacugga gacagcugcu gaacgcaaag cugaucacac agagaaaguu cgacaaccug	2700
acaaaggcag agagaggagg acugagcgaa cuggacaagg caggauucau caagagacag	2760
cuggucgaaa caagacagau cacaagcac gucgcacaga uccuggacag cagaaugaac	2820
acaaaguacg acgaaaacga caagcugauc agagaaguca aggucaucac acugaagagc	2880
aagcugguca gcgacuucag aaaggacuuc caguucuaca aggucagaga aaUCAaac	2940
uaccaccacg cacacgacgc auaccugaac gcagucgucg gaacagcacu gaucaagaag	3000
uaccgaagc uggaaagcga auucgucuac ggagacuaca aggucuacga cgucagaaag	3060
augaucgcaa agagcgaaca ggaaucgga aaggcaacag caaaguacuu cuucuacagc	3120
aacauauga acuucuuaa gacagaaauc acacuggcaa acggagaaau cagaaagaga	3180
ccgcugaucg aaacaacgg agaaacagga gaaucgucu gggacaaggg aagagacuuc	3240
gcaacaguca gaaagguccu gagcaugccg cagguaaca ucgucaagaa gacagaaguc	3300
cagacaggag gauucagcaa ggaaagcauc cugccgaaga gaaacagcga caagcugauc	3360
gcaagaaaga aggacuggga cccgaagaag uacggaggau ucgacagccc gacagucgca	3420
uacagcgucc uggucgucg aaaggucgaa aagggaaga gcaagaagcu gaagagcguc	3480
aaggaacugc ugggaaucaC aaUCAuggaa agaagcagcu ucgaaaagaa cccgaucgac	3540
uuccuggaag caaagggaua caaggaaguc aagaaggacc ugaucauaa gcugccgaag	3600
uacagccugu ucgaacugga aaacggaaga aagagaauGc uggcaagcgC aggagaacug	3660
cagaaggga acgaacuggc acugccgagc aaguacguca acuuccugua ccuggcaagc	3720
cacuacgaaa agcugaaggg aagcccgaa gacaacgaac agaagcagcu guucgucgaa	3780
cagcacaagc acuaccugga cgaaucauc gaacagauca gcgaauucag caagagaguc	3840
auccggcag acgcaaaccu ggacaagguc cugagcgau acaacaagca cagagacaag	3900
ccgaucagag aacaggcaga aaacaucauc caccuguuca cacugacaaa ccugggagca	3960
ccggcagcau ucaaguacuu cgacacaaca aucgacagaa agagauacac aagcacaag	4020
gaaguccugg acgcaacacu gauccaccag agcaucacag gacuguacga aacaagauc	4080

gaccugagcc agcugggagg agacggagga ggaagcccga agaagaagag aaaggucuag 4140

<210> 208
<211> 1379
<212> PRT
<213> Secuencia artificial

<220>
<223> Sintético: secuencia de aminoácidos de dCas9 (D10A H840A)

<400> 208

Met Asp Lys Lys Tyr Ser Ile Gly Leu Ala Ile Gly Thr Asn Ser Val
1 5 10 15

Gly Trp Ala Val Ile Thr Asp Glu Tyr Lys Val Pro Ser Lys Lys Phe
 20 25 30

Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys Lys Asn Leu Ile
 35 40 45

Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu
 50 55 60

Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys
65 70 75 80

Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met Ala Lys Val Asp Asp Ser
 85 90 95

Phe Phe His Arg Leu Glu Glu Ser Phe Leu Val Glu Glu Asp Lys Lys
 100 105 110

His Glu Arg His Pro Ile Phe Gly Asn Ile Val Asp Glu Val Ala Tyr
 115 120 125

His Glu Lys Tyr Pro Thr Ile Tyr His Leu Arg Lys Lys Leu Val Asp
 130 135 140

Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile Tyr Leu Ala Leu Ala His
145 150 155 160

Met Ile Lys Phe Arg Gly His Phe Leu Ile Glu Gly Asp Leu Asn Pro
 165 170 175

Asp Asn Ser Asp Val Asp Lys Leu Phe Ile Gln Leu Val Gln Thr Tyr

180	185	190
Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn Ala Ser Gly Val Asp Ala		
195	200	205
Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys Ser Arg Arg Leu Glu Asn		
210	215	220
Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys Asn Gly Leu Phe Gly Asn		
225	230	235 240
Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro Asn Phe Lys Ser Asn Phe		
245	250	255
Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu Ser Lys Asp Thr Tyr Asp		
260	265	270
Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile Gly Asp Gln Tyr Ala Asp		
275	280	285
Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp Ala Ile Leu Leu Ser Asp		
290	295	300
Ile Leu Arg Val Asn Thr Glu Ile Thr Lys Ala Pro Leu Ser Ala Ser		
305	310	315 320
Met Ile Lys Arg Tyr Asp Glu His His Gln Asp Leu Thr Leu Leu Lys		
325	330	335
Ala Leu Val Arg Gln Gln Leu Pro Glu Lys Tyr Lys Glu Ile Phe Phe		
340	345	350
Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr Ile Asp Gly Gly Ala Ser		
355	360	365
Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro Ile Leu Glu Lys Met Asp		
370	375	380
Gly Thr Glu Glu Leu Leu Val Lys Leu Asn Arg Glu Asp Leu Leu Arg		
385	390	395 400
Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile Pro His Gln Ile His Leu		
405	410	415

Gly Glu Leu His Ala Ile Leu Arg Arg Gln Glu Asp Phe Tyr Pro Phe
420 425 430

Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile
435 440 445

Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp
450 455 460

Met Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu
465 470 475 480

Val Val Asp Lys Gly Ala Ser Ala Gln Ser Phe Ile Glu Arg Met Thr
485 490 495

Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys Val Leu Pro Lys His Ser
500 505 510

Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu Leu Thr Lys Val Lys
515 520 525

Tyr Val Thr Glu Gly Met Arg Lys Pro Ala Phe Leu Ser Gly Glu Gln
530 535 540

Lys Lys Ala Ile Val Asp Leu Leu Phe Lys Thr Asn Arg Lys Val Thr
545 550 555 560

Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp
565 570 575

Ser Val Glu Ile Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu Gly
580 585 590

Thr Tyr His Asp Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp
595 600 605

Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile Val Leu Thr Leu Thr
610 615 620

Leu Phe Glu Asp Arg Glu Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala
625 630 635 640

His Leu Phe Asp Asp Lys Val Met Lys Gln Leu Lys Arg Arg Arg Tyr
645 650 655

Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp
660 665 670

Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe
675 680 685

Ala Asn Arg Asn Phe Met Gln Leu Ile His Asp Asp Ser Leu Thr Phe
690 695 700

Lys Glu Asp Ile Gln Lys Ala Gln Val Ser Gly Gln Gly Asp Ser Leu
705 710 715 720

His Glu His Ile Ala Asn Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly
725 730 735

Ile Leu Gln Thr Val Lys Val Val Asp Glu Leu Val Lys Val Met Gly
740 745 750

Arg His Lys Pro Glu Asn Ile Val Ile Glu Met Ala Arg Glu Asn Gln
755 760 765

Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu Arg Met Lys Arg Ile
770 775 780

Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile Leu Lys Glu His Pro
785 790 795 800

Val Glu Asn Thr Gln Leu Gln Asn Glu Lys Leu Tyr Leu Tyr Tyr Leu
805 810 815

Gln Asn Gly Arg Asp Met Tyr Val Asp Gln Glu Leu Asp Ile Asn Arg
820 825 830

Leu Ser Asp Tyr Asp Val Asp Ala Ile Val Pro Gln Ser Phe Leu Lys
835 840 845

Asp Asp Ser Ile Asp Asn Lys Val Leu Thr Arg Ser Asp Lys Asn Arg
850 855 860

Gly Lys Ser Asp Asn Val Pro Ser Glu Glu Val Val Lys Lys Met Lys
865 870 875 880

Asn Tyr Trp Arg Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys
885 890 895

Phe Asp Asn Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp
900 905 910

Lys Ala Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr
915 920 925

Lys His Val Ala Gln Ile Leu Asp Ser Arg Met Asn Thr Lys Tyr Asp
930 935 940

Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys Ser
945 950 955 960

Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys Val Arg
965 970 975

Glu Ile Asn Asn Tyr His His Ala His Asp Ala Tyr Leu Asn Ala Val
980 985 990

Val Gly Thr Ala Leu Ile Lys Lys Tyr Pro Lys Leu Glu Ser Glu Phe
995 1000 1005

Val Tyr Gly Asp Tyr Lys Val Tyr Asp Val Arg Lys Met Ile Ala
1010 1015 1020

Lys Ser Glu Gln Glu Ile Gly Lys Ala Thr Ala Lys Tyr Phe Phe
1025 1030 1035

Tyr Ser Asn Ile Met Asn Phe Phe Lys Thr Glu Ile Thr Leu Ala
1040 1045 1050

Asn Gly Glu Ile Arg Lys Arg Pro Leu Ile Glu Thr Asn Gly Glu
1055 1060 1065

Thr Gly Glu Ile Val Trp Asp Lys Gly Arg Asp Phe Ala Thr Val
1070 1075 1080

Arg Lys Val Leu Ser Met Pro Gln Val Asn Ile Val Lys Lys Thr
1085 1090 1095

Glu Val Gln Thr Gly Gly Phe Ser Lys Glu Ser Ile Leu Pro Lys
1100 1105 1110

Arg Asn Ser Asp Lys Leu Ile Ala Arg Lys Lys Asp Trp Asp Pro

1115	1120	1125
Lys Lys Tyr Gly Gly Phe Asp Ser Pro Thr Val Ala Tyr Ser Val		
1130	1135	1140
Leu Val Val Ala Lys Val Glu Lys Gly Lys Ser Lys Lys Leu Lys		
1145	1150	1155
Ser Val Lys Glu Leu Leu Gly Ile Thr Ile Met Glu Arg Ser Ser		
1160	1165	1170
Phe Glu Lys Asn Pro Ile Asp Phe Leu Glu Ala Lys Gly Tyr Lys		
1175	1180	1185
Glu Val Lys Lys Asp Leu Ile Ile Lys Leu Pro Lys Tyr Ser Leu		
1190	1195	1200
Phe Glu Leu Glu Asn Gly Arg Lys Arg Met Leu Ala Ser Ala Gly		
1205	1210	1215
Glu Leu Gln Lys Gly Asn Glu Leu Ala Leu Pro Ser Lys Tyr Val		
1220	1225	1230
Asn Phe Leu Tyr Leu Ala Ser His Tyr Glu Lys Leu Lys Gly Ser		
1235	1240	1245
Pro Glu Asp Asn Glu Gln Lys Gln Leu Phe Val Glu Gln His Lys		
1250	1255	1260
His Tyr Leu Asp Glu Ile Ile Glu Gln Ile Ser Glu Phe Ser Lys		
1265	1270	1275
Arg Val Ile Leu Ala Asp Ala Asn Leu Asp Lys Val Leu Ser Ala		
1280	1285	1290
Tyr Asn Lys His Arg Asp Lys Pro Ile Arg Glu Gln Ala Glu Asn		
1295	1300	1305
Ile Ile His Leu Phe Thr Leu Thr Asn Leu Gly Ala Pro Ala Ala		
1310	1315	1320
Phe Lys Tyr Phe Asp Thr Thr Ile Asp Arg Lys Arg Tyr Thr Ser		
1325	1330	1335

Thr Lys Glu Val Leu Asp Ala Thr Leu Ile His Gln Ser Ile Thr
1340 1345 1350

Gly Leu Tyr Glu Thr Arg Ile Asp Leu Ser Gln Leu Gly Gly Asp
1355 1360 1365

Gly Gly Gly Ser Pro Lys Lys Lys Arg Lys Val
1370 1375

<210> 209
<211> 4140
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: ORF del ARNm de dCas9 (D10A H840A)

<400> 209
auggacaaga aguacagcau cggacuggca aucggaacaa acagcgucgg augggcaguc 60
aucacagacg aauacaaggu cccgagcaag aaguucaagg uccugggaaa cacagacaga 120
cacagcauca agaagaaccu gaucggagca cugcuguucg acagcggaga aacagcagaa 180
gcaacaagac ugaagagaac agcaagaaga agauacacaa gaagaaagaa cagaaucugc 240
uaccugcagg aaaucuucag caacgaaaug gcaaaggucg acgacagcuu cuuccacaga 300
cuggaagaaa gcuuccuggu cgaagaagac aagaagcacg aaagacaccc gaucuucgga 360
aauaucgucg acgaagucgc auaccacgaa aaguacccga caaucuacca ccugagaaag 420
aagcuggucg acagcacaga caaggcagac cugagacuga ucuaccuggc acuggcacac 480
augaucaagu ucagaggaca cuuccugauc gaaggagacc ugaacccgga caacagcgac 540
gucgacaagc uguucaucca gcugguccag acauacaacc agcuguucga agaaaacccg 600
aucaacgcaa gcggagucga cgcaaaggca auccugagcg caagacugag caagagcaga 660
agacuggaaa accugaucgc acagcugccg ggagaaaaga agaacggacu guucggaaac 720
cugaucgcac ugagccuggg acugacaccg aacuuaaga gcaacuucga ccuggcagaa 780
gacgcaaagc ugcagcugag caaggacaca uacgacgacg accuggacaa ccugcuggca 840
cagaucggag accaguacgc agaccuguuc cuggcagcaa agaaccugag cgacgcaauc 900
cugcugagcg acauccugag agucaacaca gaaucacaa aggcaccgcu gagcgcaagc 960
augaucaaga gauacgacga acaccaccag gaccugacac ugcugaaggc acuggucaga 1020
cagcagcugc cggaaaagua caaggaaauc uucuucgacc agagcaagaa cggauacgca 1080
ggauacaucg acggaggagc aagccaggaa gaauucuaca aguucauca gccgauccug 1140

gaaaagaugg acggaacaga agaacugcug gucaagcuga acagagaaga ccugcugaga 1200
 aagcagagaa cauucgacaa cggaagcauc ccgcaccaga uccaccuggg agaacugcac 1260
 gcaauccuga gaagacagga agacuucuac ccguuccuga aggacaacag agaaaagauc 1320
 gaaaagaucc ugacauucag aaucccguaac uacgucggac cgcuggcaag aggaaacagc 1380
 agauucgcau ggauagacaag aaagagcgaa gaaacaauca caccguggaa cuucgaagaa 1440
 gucguccaga agggagcaag cgcacagagc uucaucgaaa gaaugacaaa cuucgacaag 1500
 aaccugccga acgaaaaggu ccugccgaag cacagccugc uguacgaaua cuucacaguc 1560
 uacaacgaac ugacaaaggu caaguacguc acagaaggaa ugagaaagcc ggcauuccug 1620
 agcggagAAC agaagaaggc aaucgucgac cugcuguuca agacaaacag aaaggucaca 1680
 gucaagcagc ugaaggaaga cuacuucaag aagaucgaau gcuucgacag cgucgaauc 1740
 agcggagucg aagacagauu caacgcaagc cugggaacau accacgaccu gcugaagauc 1800
 aucaaggaca aggacuuccu ggacaacgaa gaaaacgaag acauccugga agacaucguc 1860
 cugacacuga cacuguucga agacagagaa augaucgaag aaagacugaa gacauacgca 1920
 caccuguucg acgacaaggu caugaagcag cugaagagaa gaagauacac aggaugggga 1980
 agacugagca gaaagcugau caacggaauc agagacaagc agagcggaaa gacaauccug 2040
 gacuuccuga agagcgacgg auucgcaaac agaaacuua ugcagcugau ccacgacgac 2100
 agccugacau ucaaggaaga cauccagaag gcacagguca gcggacaggg agacagccug 2160
 cacgaacaca ucgcaaaccu ggcaaggagc ccggcaauca agaagggaau ccugcagaca 2220
 gucaaggucg ugcacgaacu gguaagguc augggaagac acaagccgga aaacaucguc 2280
 aucgaaaugg caagagaaaa ccagacaaca cagaaggagc agaagaacag cagagaaaga 2340
 augaagagaa ucgaagaagg aaucaggaa cugggaagcc agauccugaa ggaacacccg 2400
 gucgaaaaca cacagcugca gaacgaaaag cuguaccugu acuaccugca gaacggaaga 2460
 gacauguacg ugcaccagga acuggacauc aacagacuga gcgacuacga cgucgacgca 2520
 aucguccgc agagcuuccu gaaggacgac agcaucgaca acaagguccu gacaagaagc 2580
 gacaagaaca gaggaagag cgacaacguc ccgagcgaag aagucgucaa gaagaugaag 2640
 aacuacugga gacagcugcu gaacgcaaag cugaucacac agagaaaguu cgacaaccug 2700
 acaaaggcag agagaggagg acugagcgaa cuggacaagg caggauucau caagagacag 2760
 cuggucgaaa caagacagau cacaagcac gucgcacaga uccuggacag cagaaugaac 2820
 acaaaguacg acgaaaacga caagcugauc agagaaguca aggucaucac acugaagagc 2880
 aagcugguca gcgacuucag aaaggacuuc caguucuaca agguagaga aaucacaac 2940

uaccaccacg cacacgacgc auaccugaac gcagucgucg gaacagcacu gaucaagaag	3000
uacccgaagc uggaaagcga auucgucuac ggagacuaca aggucuacga cgucagaaag	3060
augaucgcaa agagcgaaca ggaaucgga aaggcaacag caaguacuu cuucuacagc	3120
aacauauga acuucuucaa gacagaaauc acacuggcaa acggagaaau cagaaagaga	3180
ccgcugaucg aaacaaacgg agaaacagga gaaucgucu gggacaaggg aagagacuuc	3240
gcaacaguca gaaagguccu gagcaugccg caggucaaca ucgucaagaa gacagaaguc	3300
cagacaggag gauucagcaa ggaaagcauc cugccgaaga gaaacagcga caagcugauc	3360
gcaagaaaga aggacuggga cccgaagaag uacggaggau ucgacagccc gacagucgca	3420
uacagcgucc uggucgucg aaaggucgaa aagggaaga gcaagaagcu gaagagcguc	3480
aaggaacugc ugggaucac aaucaggaa agaagcagcu ucgaaaagaa cccgaucgac	3540
uuccuggaag caaagggauc caaggaaguc aagaaggacc ugaucauca gcuccgaag	3600
uacagccugu ucgaacugga aaacggaaga aagagaauc uggcaagcg aggagaacug	3660
cagaaggga acgaacuggc acugccgagc aaguacguca acuuccugua ccuggcaagc	3720
cacuacgaaa agcugaaggg aagcccggaa gacaacgaac agaagcagcu guucgucgaa	3780
cagcacaagc acuaccugga cgaaucauc gaacagauca gcgaauucag caagagaguc	3840
auccuggcag acgcaaaccu ggacaagguc cugagcgcau acaacaagca cagagacaag	3900
ccgaucagag aacaggcaga aaacaucauc caccuguuca cacugacaaa ccugggagca	3960
ccggcagcau ucaaguacuu cgacacaaca aucgacagaa agagauacac aagcacaag	4020
gaaguccugg acgcaacacu gauccaccag agcaucacag gacuguacga aacaagauc	4080
gaccugagcc agcugggagg agacggagga ggaagcccga agaagaagag aaaggucuag	4140

<210> 210

<211> 4134

<212> ARN

<213> Secuencia artificial

<220>

<223> Sintético: secuencia de codificación de ARNm de Cas9 que usa codones de mínina uridina (sin codones de inicio y parada; adecuada para su inclusión en la secuencia de codificación de proteínas de fusión)

<400> 210

gacaagaagu acagcaucgg acuggacauc ggaacaaaca gcgucggaug ggcagucauc	60
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acagacgaau acaaggucc gagcaagaag uucaaggucc ugggaaacac agacagacac	120
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agcaucaaga agaaccugau cggagcacug cuguucgaca gcggagaaac agcagaagca	180
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acaagacuga agagaacagc aagaagaaga uacacaagaa gaaagaacag aaucugcuac	240
cugcaggaaa ucuucagcaa cgaaauggca aaggucgacg acagcuucuu ccacagacug	300
gaagaaagcu uccuggucga agaagacaag aagcacgaaa gacacccgau cuucggaaac	360
aucgucgacg aagucgcaua ccacgaaaag uacccgacaa ucuaccaccu gagaaagaag	420
cuggucgaca gcacagacaa ggacagaccug agacugaucu accuggcacu ggcacacaug	480
aucaaguuca gaggacacuu ccugaucgaa ggagaccuga acccggacaa cagcgacguc	540
gacaagcugu ucauccagcu gguccagaca uacaaccagc uguucgaaga aaaccgauc	600
aacgcaagcg gagucgacgc aaaggcaauc cugagcgcaa gacugagcaa gagcagaaga	660
cuggaaaacc ugaucgcaca gcugccggga gaaaagaaga acggacuguu cggaaccug	720
aucgcacuga gccugggacu gacaccgaac uucaagagca acuucgaccu ggagaagac	780
gcaaagcugc agcugagcaa ggacacauac gacgacgacc uggacaaccu gcuggcacag	840
aucggagacc aguacgcaga ccuguuccug gcagcaaaga accugagcga cgcaauccug	900
cugagcgaca uccugagagu caacacagaa aucacaaagg caccgcugag cgcaagcaug	960
aucaagagau acgacgaaca ccaccaggac cugacacugc ugaaggcacu ggucagacag	1020
cagcugccgg aaaaguacaa ggaaaucuuc uucgaccaga gcaagaacgg auacgcagga	1080
uacaucgacg gaggagcaag ccaggaagaa uucuacaagu ucaucaagcc gauccuggaa	1140
aagauggacg gaacagaaga acugcugguc aagcugaaca gagaagaccu gcugagaaag	1200
cagagaacau ugcacaacgg aagcaucccg caccagaucc accugggaga acugcacgca	1260
auccugagaa gacaggaaga cuucuacccg uuccugaagg acaacagaga aaagaucgaa	1320
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<210> 211

<211> 4134

<212> ARN

<213> Secuencia artificial

<220>

<223> Sintético: secuencia de codificación desnuda de la nickasa Cas9

<400> 211

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acaagacuga agagaacagc aagaagaaga uacacaagaa gaaagaacag aaucugcuac 240
cugcaggaaa ucuucagcaa cgaauggca aaggucgacg acagcuucuu ccacagacug 300
gaagaaagcu uccuggucga agaagacaag aagcacgaaa gacacccgau cuucggaaac 360
aucgucgacg aagucgcaua ccacgaaaag uacccgacaa ucuaccaccu gagaaagaag 420
cuggucgaca gcacagacaa ggcagaccug agacugaucu accuggcacu ggcacacaug 480
aucaaguuca gaggacacuu ccugaucgaa ggagaccuga acccggacaa cagcgacguc 540
gacaagcugu ucauccagcu gguccagaca uacaaccagc uguucgaaga aaacccgauc 600
aacgcaagcg gagucgacgc aaaggcauc cugagcgcaa gacugagcaa gagcagaaga 660
cuggaaaacc ugaucgcaca gcugccggga gaaaagaaga acggacuguu cggaaccug 720
aucgcacuga gccugggacu gacaccgaac uucaagagca acuucgaccu ggcagaagac 780
gcaaagcugc agcugagcaa ggacacauac gacgacgacc uggacaaccu gcuggcacag 840
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cagcugccgg aaaaguacaa ggaaaucuuc uucgaccaga gcaagaacgg auacgcagga 1080

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<210> 212

<211> 4134

<212> ARN

<213> Secuencia artificial

<220>

<223> Sintético: secuencia de codificación desnuda de dCas9

<400> 212

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agcaucaaga agaaccugau cggagcacug cuguucgaca gcggagaaac agcagaagca 180

acaagacuga agagaacagc aagaagaaga uacacaagaa gaaagaacag aaucugcuac	240
cugcaggaaa ucuucagcaa cgaaauggca aaggucgacg acagcuucuu ccacagacug	300
gaagaaagcu uccuggucga agaagacaag aagcacgaaa gacacccgau cuucggaaac	360
aucgucgacg aagucgcaua ccacgaaaag uacccgacaa ucuaccaccu gagaaagaag	420
cuggucgaca gcacagacaa ggacagaccug agacugaucu accuggcacu ggcacacaug	480
aucaaguuca gaggacacuu ccugaucgaa ggagaccuga acccggacaa cagcgacguc	540
gacaagcugu ucauccagcu gguccagaca uacaaccagc uguucgaaga aaacccgauc	600
aacgcaagcg gagucgacgc aaaggcaauc cugagcgcaa gacugagcaa gagcagaaga	660
cuggaaaacc ugaucgcaca gcugccggga gaaaagaaga acggacuguu cggaaccug	720
aucgcacuga gccugggacu gacaccgaac uucaagagca acuucgaccu ggcagaagac	780
gcaaagcugc agcugagcaa ggacacauac gacgacgacc uggacaaccu gcuggcacag	840
aucggagacc aguacgcaga ccuguuccug gcagcaaaga accugagcga cgcaauccug	900
cugagcgaca uccugagagu caacacagaa aucacaaagg caccgcugag cgcaagcaug	960
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<210> 213
<211> 1368
<212> PRT
<213> Secuencia artificial

<220>
<223> Sintético: Secuencia de aminoácidos de Cas9 (sin NLS)

<400> 213

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Gly Trp Ala Val Ile Thr Asp Glu Tyr Lys Val Pro Ser Lys Lys Phe
20 25 30

Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys Lys Asn Leu Ile
35 40 45

Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu
50 55 60

Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys
65 70 75 80

Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met Ala Lys Val Asp Asp Ser
85 90 95

Phe Phe His Arg Leu Glu Glu Ser Phe Leu Val Glu Glu Asp Lys Lys
100 105 110

His Glu Arg His Pro Ile Phe Gly Asn Ile Val Asp Glu Val Ala Tyr
115 120 125

His Glu Lys Tyr Pro Thr Ile Tyr His Leu Arg Lys Lys Leu Val Asp

130	135	140
Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile Tyr Leu Ala Leu Ala His		
145	150	155 160
Met Ile Lys Phe Arg Gly His Phe Leu Ile Glu Gly Asp Leu Asn Pro		
	165	170 175
Asp Asn Ser Asp Val Asp Lys Leu Phe Ile Gln Leu Val Gln Thr Tyr		
	180	185 190
Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn Ala Ser Gly Val Asp Ala		
	195	200 205
Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys Ser Arg Arg Leu Glu Asn		
	210	215 220
Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys Asn Gly Leu Phe Gly Asn		
	225	230 235 240
Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro Asn Phe Lys Ser Asn Phe		
	245	250 255
Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu Ser Lys Asp Thr Tyr Asp		
	260	265 270
Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile Gly Asp Gln Tyr Ala Asp		
	275	280 285
Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp Ala Ile Leu Leu Ser Asp		
	290	295 300
Ile Leu Arg Val Asn Thr Glu Ile Thr Lys Ala Pro Leu Ser Ala Ser		
	305	310 315 320
Met Ile Lys Arg Tyr Asp Glu His His Gln Asp Leu Thr Leu Leu Lys		
	325	330 335
Ala Leu Val Arg Gln Gln Leu Pro Glu Lys Tyr Lys Glu Ile Phe Phe		
	340	345 350
Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr Ile Asp Gly Gly Ala Ser		
	355	360 365

Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro Ile Leu Glu Lys Met Asp
370 375 380

Gly Thr Glu Glu Leu Leu Val Lys Leu Asn Arg Glu Asp Leu Leu Arg
385 390 395 400

Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile Pro His Gln Ile His Leu
405 410 415

Gly Glu Leu His Ala Ile Leu Arg Arg Gln Glu Asp Phe Tyr Pro Phe
420 425 430

Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile
435 440 445

Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp
450 455 460

Met Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu
465 470 475 480

Val Val Asp Lys Gly Ala Ser Ala Gln Ser Phe Ile Glu Arg Met Thr
485 490 495

Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys Val Leu Pro Lys His Ser
500 505 510

Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu Leu Thr Lys Val Lys
515 520 525

Tyr Val Thr Glu Gly Met Arg Lys Pro Ala Phe Leu Ser Gly Glu Gln
530 535 540

Lys Lys Ala Ile Val Asp Leu Leu Phe Lys Thr Asn Arg Lys Val Thr
545 550 555 560

Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp
565 570 575

Ser Val Glu Ile Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu Gly
580 585 590

Thr Tyr His Asp Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp
595 600 605

Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile Val Leu Thr Leu Thr
610 615 620

Leu Phe Glu Asp Arg Glu Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala
625 630 635 640

His Leu Phe Asp Asp Lys Val Met Lys Gln Leu Lys Arg Arg Arg Tyr
 645 650 655

Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp
 660 665 670

Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe
 675 680 685

Ala Asn Arg Asn Phe Met Gln Leu Ile His Asp Asp Ser Leu Thr Phe
 690 695 700

Lys Glu Asp Ile Gln Lys Ala Gln Val Ser Gly Gln Gly Asp Ser Leu
705 710 715 720

His Glu His Ile Ala Asn Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly
 725 730 735

Ile Leu Gln Thr Val Lys Val Val Asp Glu Leu Val Lys Val Met Gly
 740 745 750

Arg His Lys Pro Glu Asn Ile Val Ile Glu Met Ala Arg Glu Asn Gln
 755 760 765

Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu Arg Met Lys Arg Ile
 770 775 780

Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile Leu Lys Glu His Pro
785 790 795 800

Val Glu Asn Thr Gln Leu Gln Asn Glu Lys Leu Tyr Leu Tyr Tyr Leu
 805 810 815

Gln Asn Gly Arg Asp Met Tyr Val Asp Gln Glu Leu Asp Ile Asn Arg
 820 825 830

Leu Ser Asp Tyr Asp Val Asp His Ile Val Pro Gln Ser Phe Leu Lys
 835 840 845

Asp Asp Ser Ile Asp Asn Lys Val Leu Thr Arg Ser Asp Lys Asn Arg
850 855 860

Gly Lys Ser Asp Asn Val Pro Ser Glu Glu Val Val Lys Lys Met Lys
865 870 875 880

Asn Tyr Trp Arg Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys
885 890 895

Phe Asp Asn Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp
900 905 910

Lys Ala Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr
915 920 925

Lys His Val Ala Gln Ile Leu Asp Ser Arg Met Asn Thr Lys Tyr Asp
930 935 940

Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys Ser
945 950 955 960

Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys Val Arg
965 970 975

Glu Ile Asn Asn Tyr His His Ala His Asp Ala Tyr Leu Asn Ala Val
980 985 990

Val Gly Thr Ala Leu Ile Lys Lys Tyr Pro Lys Leu Glu Ser Glu Phe
995 1000 1005

Val Tyr Gly Asp Tyr Lys Val Tyr Asp Val Arg Lys Met Ile Ala
1010 1015 1020

Lys Ser Glu Gln Glu Ile Gly Lys Ala Thr Ala Lys Tyr Phe Phe
1025 1030 1035

Tyr Ser Asn Ile Met Asn Phe Phe Lys Thr Glu Ile Thr Leu Ala
1040 1045 1050

Asn Gly Glu Ile Arg Lys Arg Pro Leu Ile Glu Thr Asn Gly Glu
1055 1060 1065

Thr Gly Glu Ile Val Trp Asp Lys Gly Arg Asp Phe Ala Thr Val

1070	1075	1080
Arg Lys Val Leu Ser Met Pro	Gln Val Asn Ile Val	Lys Lys Thr
1085	1090	1095
Glu Val Gln Thr Gly Gly Phe	Ser Lys Glu Ser Ile	Leu Pro Lys
1100	1105	1110
Arg Asn Ser Asp Lys Leu Ile	Ala Arg Lys Lys Asp	Trp Asp Pro
1115	1120	1125
Lys Lys Tyr Gly Gly Phe Asp	Ser Pro Thr Val Ala	Tyr Ser Val
1130	1135	1140
Leu Val Val Ala Lys Val Glu	Lys Gly Lys Ser Lys	Lys Leu Lys
1145	1150	1155
Ser Val Lys Glu Leu Leu Gly	Ile Thr Ile Met Glu	Arg Ser Ser
1160	1165	1170
Phe Glu Lys Asn Pro Ile Asp	Phe Leu Glu Ala Lys	Gly Tyr Lys
1175	1180	1185
Glu Val Lys Lys Asp Leu Ile	Ile Lys Leu Pro Lys	Tyr Ser Leu
1190	1195	1200
Phe Glu Leu Glu Asn Gly Arg	Lys Arg Met Leu Ala	Ser Ala Gly
1205	1210	1215
Glu Leu Gln Lys Gly Asn Glu	Leu Ala Leu Pro Ser	Lys Tyr Val
1220	1225	1230
Asn Phe Leu Tyr Leu Ala Ser	His Tyr Glu Lys Leu	Lys Gly Ser
1235	1240	1245
Pro Glu Asp Asn Glu Gln Lys	Gln Leu Phe Val Glu	Gln His Lys
1250	1255	1260
His Tyr Leu Asp Glu Ile Ile	Glu Gln Ile Ser Glu	Phe Ser Lys
1265	1270	1275
Arg Val Ile Leu Ala Asp Ala	Asn Leu Asp Lys Val	Leu Ser Ala
1280	1285	1290

Tyr Asn Lys His Arg Asp Lys Pro Ile Arg Glu Gln Ala Glu Asn
1295 1300 1305

Ile Ile His Leu Phe Thr Leu Thr Asn Leu Gly Ala Pro Ala Ala
1310 1315 1320

Phe Lys Tyr Phe Asp Thr Thr Ile Asp Arg Lys Arg Tyr Thr Ser
1325 1330 1335

Thr Lys Glu Val Leu Asp Ala Thr Leu Ile His Gln Ser Ile Thr
1340 1345 1350

Gly Leu Tyr Glu Thr Arg Ile Asp Leu Ser Gln Leu Gly Gly Asp
1355 1360 1365

<210> 214
<211> 4107
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: ORF del ARNm de Cas9 que codifica la SEQ ID NO: 213 que usa codones de mínima uridina, con codones de inicio y parada

<400> 214
auggacaaga aguacagcau cggacuggac aucggaacaa acagcgucgg augggcaguc 60
aucacagacg aauacaaggu cccgagcaag aaguucaagg uccugggaaa cacagacaga 120
cacagcauca agaagaaccu gaucggagca cugcuguucg acagcggaga aacagcagaa 180
gcaacaagac ugaagagaac agcaagaaga agauacacaa gaagaaagaa cagaaucugc 240
uaccugcagg aaaucuucag caacgaaaug gcaaaggucg acgacagcuu cuuccacaga 300
cuggaagaaa gcuuccuggu cgaagaagac aagaagcacg aaagacaccc gaucuucgga 360
aacaucgucg acgaagucgc auaccacgaa aaguacccga caaucuacca ccugagaaaag 420
aagcuggucg acagcacaga caaggcagac cugagacuga ucuaccuggc acuggcacac 480
augaucaagu ucagaggaca cuuccugauc gaaggagacc ugaacccgga caacagcgac 540
gucgacaagc uguucaucca gcugguccag acauacaacc agcuguucga agaaaacccg 600
aucaacgcaa gcggagucga cgcaaaggca auccugagcg caagacugag caagagcaga 660
agacuggaaa accugaucgc acagcugccg ggagaaaaga agaacggacu guucggaaac 720
cugaucgcac ugagccuggg acugacaccg aacuucaaga gcaacuucga ccuggcagaa 780
gacgcaaagc ugcagcugag caaggacaca uacgacgacg accuggacaa ccugcuggca 840
cagaucggag accaguacgc agaccuguuc cuggcagcaa agaaccugag cgacgcaauc 900

cugcugagcg acauccugag agucaacaca gaaaucacaa aggcaccgcu gagcgcaagc	960
augaucaaga gauacgacga acaccaccag gaccugacac ugcugaaggc acuggucaga	1020
cagcagcugc cggaaaagua caaggaaauc uucuucgacc agagcaagaa cggauacgca	1080
ggauacaucg acggaggagc aagccaggaa gaauucuaca aguucauaa gccgauccug	1140
gaaaagaugg acggaacaga agaacugcug gucaagcuga acagagaaga ccugcugaga	1200
aagcagagaa cauucgacaa cggaagcauc ccgcaccaga uccaccuggg agaacugcac	1260
gcaauccuga gaagacagga agacuucuac ccguuccuga aggacaacag agaaaagauc	1320
gaaaagaucc ugacauucag aaucccuac uacgucggac cgcuggcaag aggaaacagc	1380
agauucgau ggauagacaag aaagagcgaa gaaacaauc caccugggaa cuucgaagaa	1440
gucgucgaca agggagcaag cgcacagagc uucaucgaaa gaaugacaaa cuucgacaag	1500
aaccugccga acgaaaaggu ccugccgaag cacagccugc uguacgaaua cuucacaguc	1560
uacaacgaac ugacaaaggu caaguacguc acagaaggaa ugagaaagcc ggcauuccug	1620
agcggagaac agaagaaggc aaucgucgac cugcuguuca agacaaacag aaaggucaca	1680
gucaagcagc ugaaggaaga cuacuucaag aagaucgaau gcuucgacag cgucgaaauc	1740
agcggagucg aagacagauu caacgcaagc cugggaacau accacgaccu gcugaagauc	1800
aucaaggaca aggacuuccu ggacaacgaa gaaaacgaag acauccugga agacaucguc	1860
cugacacuga cacuguucga agacagagaa augaucgaag aaagacugaa gacauacgca	1920
caccuguucg acgacaaggu caugaagcag cugaagagaa gaagauacac aggaugggga	1980
agacugagca gaaagcugau caacggaauc agagacaagc agagcggaaa gacaauccug	2040
gacuuccuga agagcgacgg auucgcaaac agaaacuua ugcagcugau ccacgacgac	2100
agccugacau ucaaggaaga cauccagaag gcacagguca gcggacaggg agacagccug	2160
cacgaacaca ucgcaaaccu ggcaaggagc ccggcaauca agaagggaau ccugcagaca	2220
gucaaggucg ugcacgaacu ggucaagguc augggaagac acaagccgga aaacaucguc	2280
aucgaaaugg caagagaaaa ccagacaaca cagaaggagc agaagaacag cagagaaaga	2340
augaagagaa ucgaagaagg aaucaggaa cugggaagcc agauccugaa ggaacacccg	2400
gucgaaaaca cacagcugca gaacgaaaag cuguaccugu acuaccugca gaacggaaga	2460
gacauguacg ugcaccagga acuggacauc aacagacuga gcgacuacga cgucgaccac	2520
aucguccgc agagcuuccu gaaggacgac agcaucgaca acaagguccu gacaagaagc	2580
gacaagaaca gaggaagag cgacaacguc ccgagcgaag aagucgucaa gaagaugaag	2640

aacuacugga gacagcugcu gaacgcaaag cugaucacac agagaaaguu cgacaaccug 2700
acaaaggcag agagaggagg acugagcgaa cuggacaagg caggauucau caagagacag 2760
cuggucgaaa caagacagau cacaagcac gucgcacaga uccuggacag cagaaugaac 2820
acaaaguacg acgaaaacga caagcugauc agagaaguca aggucaucac acugaagagc 2880
aagcugguca gcgacuucag aaaggacuuc caguucuaca agguagaga aaucacaac 2940
uaccaccag cacacgacgc auaccugaac gcagucgucg gaacagcacu gaucaagaag 3000
uaccgaagc uggaaagcga auucgucuac ggagacuaca agguacuaga cgucagaaag 3060
augaucgcaa agagcgaaac ggaaucgga aaggcaacag caaguacuu cuucuacagc 3120
aacaucaga acuucuuaa gacagaaauc acacuggcaa acggagaaau cagaaagaga 3180
ccgcugaucg aaacaaacgg agaaacagga gaaucgucu gggacaaggg aagagacuuc 3240
gcaacaguca gaaagguccu gagcaugccg cagguaaca ucgucaaga gacagaaguc 3300
cagacaggag gauucagcaa ggaaagcauc cugccgaaga gaaacagcga caagcugauc 3360
gcaagaaaga aggacuggga cccgaagaag uacggaggau ucgacagccc gacagucgca 3420
uacagcgucc uggucgucg aaaggucgaa aagggaaga gcaagaagcu gaagagcguc 3480
aaggaacugc ugggaaucaac aaucaggaa agaagcagcu ucgaaaaga cccgaucgac 3540
uuccuggaag caaagggauc caaggaaguc aagaaggacc ugaucauca gcugccgaag 3600
uacagccugu ucgaacugga aaacggaaga aagagaauagc uggcaagcgaggaggacug 3660
cagaaggga acgaacuggc acugccgagc aaguacguca acuuccugua ccuggcaagc 3720
cacuacgaaa agcugaaggg aagcccgga gacaacgaac agaagcagcu guucgucgaa 3780
cagcacaagc acuaccugga cgaaucauc gaacagauca gcgaauucag caagagaguc 3840
auccuggcag acgcaaaccu ggacaagguc cugagcgcau acaacaagca cagagacaag 3900
ccgaucagag aacaggcaga aaacaucauc caccuguuca cacugacaaa ccugggagca 3960
ccggcagcau ucaaguacuu cgacacaaca aucgacagaa agagauacac aagcacaag 4020
gaaguccugg acgcaacacu gauccaccag agcaucacag gacuguacga aacaagaau 4080
gaccugagcc agcugggagg agacuag 4107

<210> 215
<211> 4101
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: secuencia de codificación de Cas9 que codifica la SEQ ID NO: 213 que usa
codones de mínima uridina (sin codones de inicio y parada; adecuada para su inclusión en

la secuencia de codificación de proteínas de fusión)

<400> 215

gacaagaagu acagcaucgg acuggacauc ggaacaaaca gcgucggaug ggcagucauc	60
acagacgaau acaagguccc gagcaagaag uucaaggucc ugaggaaacac agacagacac	120
agcaucaaga agaaccugau cggagcacug cuguucgaca gcggagaaac agcagaagca	180
acaagacuga agagaacagc aagaagaaga uacacaagaa gaaagaacag aaucugcuac	240
cugcaggaaa ucuucagcaa cgaaauggca aaggucgacg acagcuucuu ccacagacug	300
gaagaaagcu uccuggucga agaagacaag aagcacgaaa gacacccgau cuucggaaac	360
aucgucgacg aagucgcaua ccacgaaaag uaccgacaa ucuaccaccu gagaaagaag	420
cuggucgaca gcacagacaa ggcagaccug agacugaucu accuggcacu ggcacacaug	480
aucaaguuca gaggacacuu ccugaucgaa ggagaccuga acccggacaa cagcgacguc	540
gacaagcugu ucauccagcu gguccagaca uacaaccagc uguucgaaga aaacccgauc	600
aacgcaagcg gagucgacgc aaaggcauc cugagcgcaa gacugagcaa gagcagaaga	660
cuggaaaacc ugaucgcaca gcugccggga gaaaagaaga acggacuguu cggaaccug	720
aucgcacuga gccugggacu gacaccgaac uucaagagca acuucgaccu ggcagaagac	780
gcaaagcugc agcugagcaa ggacacauac gacgacgacc uggacaaccu gcuggcacag	840
aucggagacc aguacgcaga ccuguuccug gcagcaaaga accugagcga cgcaauccug	900
cugagcgaca uccugagagu caacacagaa aucacaaagg caccgcugag cgcaagcaug	960
aucaagagau acgacgaaca ccaccaggac cugacacugc ugaaggcacu ggucagacag	1020
cagcugccgg aaaaguacaa ggaauucuuc uucgaccaga gcaagaacgg auacgcagga	1080
uacaucgacg gaggagcaag ccaggaagaa uucuacaagu ucaucaagcc gauccuggaa	1140
aagauggacg gaacagaaga acugcugguc aagcugaaca gagaagaccu gcugagaaag	1200
cagagaacau ucgacaacgg aagcaucccg caccagaucc accugggaga acugcacgca	1260
auccugagaa gacaggaaga cuucuacccg uuccugaagg acaacagaga aaagaucgaa	1320
aagauccuga cauucagaau ccguacuac gucggaccgc uggcaagagg aaacagcaga	1380
uucgcaugga ugacaagaaa gagcgaagaa acaaucacac cguggaacuu cgaagaaguc	1440
gucgacaagg gagcaagcgc acagagcuuc aucgaaagaa ugacaaacuu cgacaagaac	1500
cugccgaacg aaaagguccu gccgaagcac agccugcugu acgaauacuu cacagucuac	1560
aacgaacuga caaaggucua guacgucaca gaaggaauga gaaagccggc auuccugagc	1620
ggagaacaga agaaggcaau cgucgaccug cuguucaaga caaacagaaa ggucacaguc	1680

aagcagcuga aggaagacua cuucaagaag aucgaaugcu ucgacagcgu cgaaaucagc	1740
ggagucgaag acagauuca cgcaagccug ggaacauacc acgaccugcu gaagaucauc	1800
aaggacaagg acuuccugga caacgaagaa aacgaagaca uccuggaaga caucguccug	1860
acacugacac uguucgaaga cagagaaaug aucgaagaaa gacugaagac auacgcacac	1920
cuguucgacg acaaggucan gaagcagcug aagagaagaa gauacacagg auggggaaga	1980
cugagcagaa agcugaucaa cggaucaga gacaagcaga gcggaaagac aaucuggac	2040
uuccugaaga gcgacggaau cgaaacaga aacuucagc agcugaucca cgacgacagc	2100
cugacauuca aggaagacau ccagaaggca caggucagcg gacagggaga cagccugcac	2160
gaacacaucg caaaccuggc aggaagcccg gcaaucaaga agggaauccu gcagacaguc	2220
aaggucgucg acgaacuggu caaggucan ggaagacaca agccggaaaa caucgucauc	2280
gaaauggcaa gagaaaacca gacaacacag aaggacaga agaacagcag agaaagaug	2340
aagagaaucg aagaaggau caaggacug ggaagccaga uccugaagga acaccgguc	2400
gaaaacacac agcugcagaa cgaaaagcug uaccuguacu accugcagaa cggaagagac	2460
auguacgucg accaggaacu ggacauaac agacugagcg acuacgagcu cgaccacau	2520
guccgcaga gcuuccugaa ggacgacagc aucgacaaca agguccugac aagaagcagc	2580
aagaacagag gaaagagcga caacguccc agcgaagaag ucgucaagaa gaugaagaac	2640
uacuggagac agcugcugaa cgaaagcug aucacacaga gaaaguucga caaccugaca	2700
aaggcagaga gaggaggacu gagcgaacug gacaaggcag gauucauaa gagacagcug	2760
gucgaaaca gacagauca aaagcacguc gcacagaucc uggacagcag aaugaacaca	2820
aaguacgacg aaaacgaca gcugaucaga gaagucagg ucaucacacu gaagagcaag	2880
cuggucagcg acuucagaaa ggacuuccag uucuacaagg ucagagaaau caacaacuac	2940
caccacgcac acgacgcaua ccugaacgca gucgucggaa cagcacugau caagaaguac	3000
ccgaagcugg aaagcgaau cgucucgga gacuacaagg ucuacgagcu cagaaagaug	3060
aucgcaaaga gcgaacagga aaucggaaag gcaacagcaa aguacuucu cuacagcaac	3120
aucaugaacu ucuucaagac agaaucaca cuggcaaagc gagaaucag aaagagaccg	3180
cugaucgaaa caaacggaga aacaggagaa aucgucggg acaagggaag agacuucgca	3240
acagucagaa agguccugag caugccgag gucaaucag ucaagaagac agaaguccag	3300
acaggaggau ucagcaagga aagcauccug ccgaagagaa acagcgaca gcugaucgca	3360
agaaagaagg acugggaccc gaagaaguac ggaggauucg acagccgac agucgcauac	3420
agcguccugg ucgucgaaa ggucgaaaag ggaaagagca agaagcugaa gagcgucaag	3480

gaacugcugg gaaucaaaau cauggaaaga agcagcuucg aaaagaaccc gaucgacuuc 3540
cuggaagcaa agggauacaa ggaagucaag aaggaccuga ucaucaagcu gccgaaguac 3600
agccuguucg aacuggaaaa cggaagaaag agaaugcugg caagcgcagg agaacugcag 3660
aagggaacg aacuggcacu gccgagcaag uacgucaacu uccuguaccu ggcaagccac 3720
uacgaaaagc ugaagggaag cccggaagac aacgaacaga agcagcuguu cgucgaacag 3780
cacaagcacu accuggacga aaucaucgaa cagaucagcg aaucagcaa gagagucauc 3840
cuggcagacg caaaccugga caagguccug agcgcauaca acaagcacag agacaagccg 3900
aucagagaac aggcagaaaa caucauccac cuguucacac ugacaaaccu gggagcaccg 3960
gcagcauua aguacuucga cacaacauc gacagaaaga gauacacaag cacaaggaa 4020
guccuggacg caacacugau ccaccagagc aucacaggac uguacgaaac aagaucgac 4080
cugagccagc ugggaggaga c 4101

<210> 216
<211> 1368
<212> PRT
<213> Secuencia artificial

<220>
<223> Sintético: secuencia de aminoácidos de la nickasa Cas9 (sin NLS)

<400> 216

Met Asp Lys Lys Tyr Ser Ile Gly Leu Ala Ile Gly Thr Asn Ser Val
1 5 10 15

Gly Trp Ala Val Ile Thr Asp Glu Tyr Lys Val Pro Ser Lys Lys Phe
20 25 30

Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys Lys Asn Leu Ile
35 40 45

Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu
50 55 60

Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys
65 70 75 80

Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met Ala Lys Val Asp Asp Ser
85 90 95

Phe Phe His Arg Leu Glu Glu Ser Phe Leu Val Glu Glu Asp Lys Lys

100	105	110
His Glu Arg His Pro Ile Phe Gly Asn Ile Val Asp Glu Val Ala Tyr		
115	120	125
His Glu Lys Tyr Pro Thr Ile Tyr His Leu Arg Lys Lys Leu Val Asp		
130	135	140
Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile Tyr Leu Ala Leu Ala His		
145	150	155 160
Met Ile Lys Phe Arg Gly His Phe Leu Ile Glu Gly Asp Leu Asn Pro		
165	170	175
Asp Asn Ser Asp Val Asp Lys Leu Phe Ile Gln Leu Val Gln Thr Tyr		
180	185	190
Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn Ala Ser Gly Val Asp Ala		
195	200	205
Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys Ser Arg Arg Leu Glu Asn		
210	215	220
Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys Asn Gly Leu Phe Gly Asn		
225	230	235 240
Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro Asn Phe Lys Ser Asn Phe		
245	250	255
Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu Ser Lys Asp Thr Tyr Asp		
260	265	270
Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile Gly Asp Gln Tyr Ala Asp		
275	280	285
Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp Ala Ile Leu Leu Ser Asp		
290	295	300
Ile Leu Arg Val Asn Thr Glu Ile Thr Lys Ala Pro Leu Ser Ala Ser		
305	310	315 320
Met Ile Lys Arg Tyr Asp Glu His His Gln Asp Leu Thr Leu Leu Lys		
325	330	335

Ala Leu Val Arg Gln Gln Leu Pro Glu Lys Tyr Lys Glu Ile Phe Phe
340 345 350

Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr Ile Asp Gly Gly Ala Ser
355 360 365

Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro Ile Leu Glu Lys Met Asp
370 375 380

Gly Thr Glu Glu Leu Leu Val Lys Leu Asn Arg Glu Asp Leu Leu Arg
385 390 395 400

Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile Pro His Gln Ile His Leu
405 410 415

Gly Glu Leu His Ala Ile Leu Arg Arg Gln Glu Asp Phe Tyr Pro Phe
420 425 430

Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile
435 440 445

Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp
450 455 460

Met Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu
465 470 475 480

Val Val Asp Lys Gly Ala Ser Ala Gln Ser Phe Ile Glu Arg Met Thr
485 490 495

Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys Val Leu Pro Lys His Ser
500 505 510

Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu Leu Thr Lys Val Lys
515 520 525

Tyr Val Thr Glu Gly Met Arg Lys Pro Ala Phe Leu Ser Gly Glu Gln
530 535 540

Lys Lys Ala Ile Val Asp Leu Leu Phe Lys Thr Asn Arg Lys Val Thr
545 550 555 560

Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp
565 570 575

Ser Val Glu Ile Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu Gly
580 585 590

Thr Tyr His Asp Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp
595 600 605

Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile Val Leu Thr Leu Thr
610 615 620

Leu Phe Glu Asp Arg Glu Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala
625 630 635 640

His Leu Phe Asp Asp Lys Val Met Lys Gln Leu Lys Arg Arg Arg Tyr
645 650 655

Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp
660 665 670

Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe
675 680 685

Ala Asn Arg Asn Phe Met Gln Leu Ile His Asp Asp Ser Leu Thr Phe
690 695 700

Lys Glu Asp Ile Gln Lys Ala Gln Val Ser Gly Gln Gly Asp Ser Leu
705 710 715 720

His Glu His Ile Ala Asn Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly
725 730 735

Ile Leu Gln Thr Val Lys Val Val Asp Glu Leu Val Lys Val Met Gly
740 745 750

Arg His Lys Pro Glu Asn Ile Val Ile Glu Met Ala Arg Glu Asn Gln
755 760 765

Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu Arg Met Lys Arg Ile
770 775 780

Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile Leu Lys Glu His Pro
785 790 795 800

Val Glu Asn Thr Gln Leu Gln Asn Glu Lys Leu Tyr Leu Tyr Tyr Leu
805 810 815

Gln Asn Gly Arg Asp Met Tyr Val Asp Gln Glu Leu Asp Ile Asn Arg
820 825 830

Leu Ser Asp Tyr Asp Val Asp His Ile Val Pro Gln Ser Phe Leu Lys
835 840 845

Asp Asp Ser Ile Asp Asn Lys Val Leu Thr Arg Ser Asp Lys Asn Arg
850 855 860

Gly Lys Ser Asp Asn Val Pro Ser Glu Glu Val Val Lys Lys Met Lys
865 870 875 880

Asn Tyr Trp Arg Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys
885 890 895

Phe Asp Asn Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp
900 905 910

Lys Ala Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr
915 920 925

Lys His Val Ala Gln Ile Leu Asp Ser Arg Met Asn Thr Lys Tyr Asp
930 935 940

Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys Ser
945 950 955 960

Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys Val Arg
965 970 975

Glu Ile Asn Asn Tyr His His Ala His Asp Ala Tyr Leu Asn Ala Val
980 985 990

Val Gly Thr Ala Leu Ile Lys Lys Tyr Pro Lys Leu Glu Ser Glu Phe
995 1000 1005

Val Tyr Gly Asp Tyr Lys Val Tyr Asp Val Arg Lys Met Ile Ala
1010 1015 1020

Lys Ser Glu Gln Glu Ile Gly Lys Ala Thr Ala Lys Tyr Phe Phe
1025 1030 1035

Tyr Ser Asn Ile Met Asn Phe Phe Lys Thr Glu Ile Thr Leu Ala

1040	1045	1050
Asn Gly	Glu Ile Arg Lys Arg	Pro Leu Ile Glu Thr Asn Gly Glu
1055	1060	1065
Thr Gly	Glu Ile Val Trp Asp	Lys Gly Arg Asp Phe Ala Thr Val
1070	1075	1080
Arg Lys	Val Leu Ser Met Pro	Gln Val Asn Ile Val Lys Lys Thr
1085	1090	1095
Glu Val	Gln Thr Gly Gly Phe	Ser Lys Glu Ser Ile Leu Pro Lys
1100	1105	1110
Arg Asn	Ser Asp Lys Leu Ile	Ala Arg Lys Lys Asp Trp Asp Pro
1115	1120	1125
Lys Lys	Tyr Gly Gly Phe Asp	Ser Pro Thr Val Ala Tyr Ser Val
1130	1135	1140
Leu Val	Val Ala Lys Val Glu	Lys Gly Lys Ser Lys Lys Leu Lys
1145	1150	1155
Ser Val	Lys Glu Leu Leu Gly	Ile Thr Ile Met Glu Arg Ser Ser
1160	1165	1170
Phe Glu	Lys Asn Pro Ile Asp	Phe Leu Glu Ala Lys Gly Tyr Lys
1175	1180	1185
Glu Val	Lys Lys Asp Leu Ile	Ile Lys Leu Pro Lys Tyr Ser Leu
1190	1195	1200
Phe Glu	Leu Glu Asn Gly Arg	Lys Arg Met Leu Ala Ser Ala Gly
1205	1210	1215
Glu Leu	Gln Lys Gly Asn Glu	Leu Ala Leu Pro Ser Lys Tyr Val
1220	1225	1230
Asn Phe	Leu Tyr Leu Ala Ser	His Tyr Glu Lys Leu Lys Gly Ser
1235	1240	1245
Pro Glu	Asp Asn Glu Gln Lys	Gln Leu Phe Val Glu Gln His Lys
1250	1255	1260

His Tyr Leu Asp Glu Ile Ile Glu Gln Ile Ser Glu Phe Ser Lys
1265 1270 1275

Arg Val Ile Leu Ala Asp Ala Asn Leu Asp Lys Val Leu Ser Ala
1280 1285 1290

Tyr Asn Lys His Arg Asp Lys Pro Ile Arg Glu Gln Ala Glu Asn
1295 1300 1305

Ile Ile His Leu Phe Thr Leu Thr Asn Leu Gly Ala Pro Ala Ala
1310 1315 1320

Phe Lys Tyr Phe Asp Thr Thr Ile Asp Arg Lys Arg Tyr Thr Ser
1325 1330 1335

Thr Lys Glu Val Leu Asp Ala Thr Leu Ile His Gln Ser Ile Thr
1340 1345 1350

Gly Leu Tyr Glu Thr Arg Ile Asp Leu Ser Gln Leu Gly Gly Asp
1355 1360 1365

<210> 217

<211> 4107

<212> ARN

<213> Secuencia artificial

<220>

<223> Sintético: ORF del ARNm de la nickasa Cas9 que codifica la SEQ ID NO: 216 que usa
codones de mínima uridina como se enumeran en la Tabla 3, con codones de inicio y
parada

<400> 217

auggacaaga aguacagcau cggacuggca aucggaacaa acagcgucgg augggcaguc	60
aucacagacg aaaucaaggu cccgagcaag aaguucaagg uccugggaaa cacagacaga	120
cacagcauca agaagaaccu gaucggagca cugcuguucg acagcggaga aacagcagaa	180
gcaacaagac ugaagagaac agcaagaaga agauacacaa gaagaaagaa cagaaucugc	240
uaccugcagg aaaucuucag caacgaaaug gcaaaggucg acgacagcuu cuuccacaga	300
cuggaagaaa gcuuccuggu cgaagaagac aagaagcacg aaagacaccc gaucuucgga	360
aacaucgucg acgaagucgc auaccacgaa aaguaccgca caaucuacca ccugagaaag	420
aagcuggucg acagcacaga caaggcagac cugagacuga ucuaccuggc acuggcacac	480
augaucaagu ucagaggaca cuuccugauc gaaggagacc ugaacccgga caacagcgac	540
gucgacaagc uguucaucca gcugguccag acauacaacc agcuguucga agaaaacccg	600

aucaacgcaa gcgagucga cgcaaaggca auccugagcg caagacugag caagagcaga	660
agacuggaaa accugaucgc acagcugccg ggagaaaaga agaacggacu guucggaaac	720
cugaucgcac ugagccuggg acugacaccg aacuuaaga gcaacuucga ccuggcagaa	780
gacgcaaagc ugcagcugag caaggacaca uacgacgacg accuggacaa ccugcuggca	840
cagaucggag accaguacgc agaccuguuc cuggcagcaa agaaccugag cgacgcauc	900
cugcugagcg acauccugag agucaacaca gaaaucacaa aggcaccgcu gagcgcaagc	960
augaucaaga gauacgacga acaccaccag gaccugacac ugcugaaggc acuggucaga	1020
cagcagcugc cggaaaagua caaggaaauc uucuucgacc agagcaagaa cggauacgca	1080
ggauacaucg acggaggagc aagccaggaa gaauucuaca aguucauca gccgauccug	1140
gaaaagaugg acggaacaga agaacugcug gucaagcuga acagagaaga ccugcugaga	1200
aagcagagaa cauucgacaa cggaagcauc ccgcaccaga uccaccuggg agaacugcac	1260
gcaauccuga gaagacagga agacuucuac ccguuccuga aggacaacag agaaaagauc	1320
gaaaagaucc ugacauucag aaucccgua uacgucggac cgcuggcaag aggaaacagc	1380
agauucgcau ggauagacaag aaagagcgaa gaaacaauca caccugggaa cuucgaagaa	1440
gucgucgaca agggagcaag cgcacagagc uucaucgaaa gaaugacaaa cuucgacaag	1500
aaccugccga acgaaaaggu ccugccgaag cacagccugc uguacgaaua cuucacaguc	1560
uacaacgaac ugacaaaggu caaguacguc acagaaggaa ugagaaagcc ggcauuccug	1620
agcggagaac agaagaaggc aaucgucgac cugcuguuca agacaaacag aaaggucaca	1680
gucaagcagc ugaaggaaga cuacuuaag aagaucgaau gcuucgacag cgucgaaauc	1740
agcggagucg aagacagauu caacgcaagc cugggaacau accacgaccu gcugaagauc	1800
aucaaggaca aggacuuccu ggacaacgaa gaaaacgaag acauccugga agacaucguc	1860
cugacacuga cacuguucga agacagagaa augaucgaag aaagacugaa gacauacgca	1920
caccuguucg acgacaaggu caugaagcag cugaagagaa gaagauacac aggaugggga	1980
agacugagca gaaagcugau caacggauc agagacaagc agagcggaaa gacaauccug	2040
gacuuccuga agagcgacgg auucgcaaac agaaacuua ugcagcugau ccacgacgac	2100
agccugacau ucaaggaaga cauccagaag gcacagguca gcggacaggg agacagccug	2160
cacgaacaca ucgcaaaccu ggaggaagc ccggcaauca agaagggaau ccugcagaca	2220
gucaaggucg ugcacgaacu ggucaagguc augggaagac acaagccgga aaacaucguc	2280
aucgaaaugg caagagaaaa ccagacaaca cagaagggac agaagaacag cagagaaaga	2340
augaagagaa ucgaagaagg aaucaggaa cugggaagcc agauccugaa ggaacaccg	2400

gucgaaaaca cacagcugca gaacgaaaag cuguaccugu acuaccugca gaacggaaga 2460
gacauguacg ucgaccagga acuggacauc aacagacuga gcgacuacga cgucgaccac 2520
aucguccgc agagcuuccu gaaggacgac agcaucgaca acaagguccu gacaagaagc 2580
gacaagaaca gaggaaagag cgacaacguc ccgagcgaag aagucgucaa gaagaugaag 2640
aacuacugga gacagcugcu gaacgcaaag cugaucacac agagaaaguu cgacaaccug 2700
acaaaggcag agagaggagg acugagcgaa cuggacaagg caggauucau caagagacag 2760
cuggucgaaa caagacagau cacaagcac gucgcacaga uccuggacag cagaaugaac 2820
acaaaguacg acgaaaacga caagcugauc agagaaguca aggucaucac acugaagagc 2880
aagcugguca gcgacuucag aaaggacuuc caguucuaca agguagaga aaucacaac 2940
uaccaccag cacacgacgc auaccugaac gcagucgucg gaacagcacu gaucaagaag 3000
uaccgaagc uggaaagcga auucgucuac ggagacuaca agguacuaga cgucagaaag 3060
augaucgaa agagcgaaca ggaaucgga aaggcaacag caaguacuu cuucuacagc 3120
aacaucaga acuucuuaa gacagaaauc acacuggcaa acggagaaau cagaaagaga 3180
ccgcugaucg aaacaaacgg agaaacagga gaaucgucu gggacaaggg aagagacuuc 3240
gcaacaguca gaaagguccu gagcaugccg caggucaaca ucgucaagaa gacagaaguc 3300
cagacaggag gauucagcaa ggaaagcauc cugccgaaga gaaacagcga caagcugauc 3360
gcaagaaaga aggacuggga cccgaagaag uacggaggau ucgacagccc gacagucgca 3420
uacagcgucc uggucgucg aaaggucgaa aagggaaga gcaagaagcu gaagagcugc 3480
aaggaacugc ugggaucac aaucaggaa agaagcagcu ucgaaaagaa cccgaucgac 3540
uuccuggaag caaagggaau caaggaaguc aagaaggacc ugaucauaa gcugccgaag 3600
uacagccugu ucgaacugga aaacggaaga aagagaagc uggcaagcg aggagaacug 3660
cagaaggga acgaacuggc acugccgagc aaguacguca acuuccugua ccuggcaagc 3720
cacuacgaaa agcugaaggg aagcccggaa gacaacgaac agaagcagcu guucgucgaa 3780
cagcacaagc acuaccugga cgaaaucauc gaacagauca gcgaauucag caagagaguc 3840
auccuggcag acgcaaaccu ggacaagguc cugagcgcau acaacaagca cagagacaag 3900
ccgaucagag aacaggcaga aaacaucauc caccuguuca cacugacaaa ccugggagca 3960
ccggcagcau ucaaguacuu cgacacaaca aucgacagaa agagauacac aagcacaag 4020
gaaguccugg acgcaacacu gauccaccag agcaucacag gacuguacga aacaagauc 4080
gaccugagcc agcugggagg agacuag

<210> 218

<211> 4101

<212> ARN

<213> Secuencia artificial

<220>

<223> Sintético: secuencia de codificación de la nickasa Cas9 que codifica la SEQ ID NO: 216 que usa codones de mínima uridina como se enumeran en la Tabla 3 (sin codones de inicio y parada; adecuada para la inclusión en la secuencia de codificación de proteínas de fusión)

<400> 218

gacaagaagu acagcaucgg acuggcaauc ggaacaaaca gcgucggaug ggcagucauc60

acagacgaau acaagguccc gagcaagaag uucaaggucc ugaggaaacac agacagacac120

agcaucaaga agaaccugau cggagcacug cuguucgaca gcggagaaac agcagaagca180

acaagacuga agagaacagc aagaagaaga uacacaagaa gaaagaacag aaucugcuac240

cugcaggaaa ucuucagcaa cgaauggca aaggucgacg acagcuucuu ccacagacug300

gaagaaagcu uccuggucga agaagacaag aagcacgaaa gacacccgau cuucggaaac360

aucgucgacg aagucgcaua ccacgaaaag uaccgacaa ucuaccaccu gagaagaag420

cuggucgaca gcacagacaa ggcagaccug agacugaucu accuggcacu ggcacacaug480

aucaaguuca gaggacacuu ccugaucgaa ggagaccuga acccgacaa cagcgacguc540

gacaagcugu ucauccagcu gguccagaca uacaaccagc uguucgaaga aaaccgauc600

aacgcaagcg gagucgacgc aaaggcauc cugagcgcaa gacugagcaa gagcagaaga660

cuggaaaacc ugauvcgaca gcugccggga gaaaagaaga acggacuguu cggaaccug720

aucgcacuga gccugggacu gacaccgaac uucaagagca acuucgaccu ggcagaagac780

gcaaagcugc agcugagcaa ggacacauac gacgacgacc uggacaaccu gcuggcacag840

aucggagacc aguacgcaga ccuguuccug gcagcaaaga accugagcga cgcaauccug900

cugagcgaca uccugagagu caacacagaa aucacaaagg caccgcugag cgcaagcaug960

aucaagagau acgacgaaca ccaccaggac cugacacugc ugaaggcacu ggucagacag1020

cagcugccgg aaaaguacaa ggaaauuc uucgaccaga gcaagaacgg auacgcagga1080

uauvcgacg gaggagcaag ccaggaagaa uucuacaagu ucaucaagcc gauccuggaa1140

aagauggacg gaacagaaga acugcugguc aagcugaaca gagaagaccu gcugagaaag1200

cagagaacau uvcacaacgg aagcaucccg caccagauc accugggaga acugcacgca1260

auccugagaa gacaggaaga cuucuacccg uuccugaagg acaacagaga aaagaucgaa1320

aagauccuga cauucagaau ccguacuac gucggaccgc uggcaagagg aaacagcaga1380

uucgcaugga ugacaagaaa gagcgaagaa acaaucacac cguggaacuu cgaagaaguc	1440
gucgacaagg gagcaagcgc acagagcuuc aucgaaagaa ugacaaacuu cgacaagaac	1500
cugccgaacg aaaagguccu gccgaagcac agccugcugu acgaauacuu cacagucuac	1560
aacgaacuga caaaggucua guacgucaca gaaggaauga gaaagccggc auuccugagc	1620
ggagaacaga agaaggcaau cgucgaccug cuguucaaga caaacagaaa ggucacaguc	1680
aagcagcuga aggaagacua cuucaagaag aucgaaugcu ucgacagcgu cgaaaucagc	1740
ggagucgaag acagauucaa cgcaagccug ggaacauacc acgaccugcu gaagaucauc	1800
aaggacaagg acuuccugga caacgaagaa aacgaagaca uccuggaaga caucguccug	1860
acacugacac uguucgaaga cagagaaaug aucgaagaaa gacugaagac auacgcacac	1920
cuguucgacg acaaggucuu gaagcagcug aagagaagaa gauacacagg auggggaaga	1980
cugagcagaa agcugaucaa cggaaucaga gacaagcaga gcggaagac aauccuggac	2040
uuccugaaga gcgacggauu cgcaaacaga aacuucaugc agcugaucca cgacgacagc	2100
cugacauuca aggaagacau ccagaaggca caggucagcg gacagggaga cagccugcac	2160
gaacacaucg caaaccuggc aggaagcccg gcaaucaaga agggaaucuu gcagacaguc	2220
aaggucgucg acgaacuggu caagguaug ggaagacaca agccggaaaa caucgucauc	2280
gaaauggcaa gagaaaacca gacaacacag aaggacaga agaacagcag agaaagaug	2340
aagagaaucg aagaaggaa caaggaacug ggaagccaga uccugaagga acacccgguc	2400
gaaaacacac agcugcagaa cgaaaagcug uaccuguacu accugcagaa cggaagagac	2460
auguacgucg accaggaacu ggacaucaac agacugagcg acuacgacgu cgaccacau	2520
guccgcaga gcuuccugaa ggacgacagc aucgacaaca agguccugac aagaagcagc	2580
aagaacagag gaaagagcga caacgucccg agcgaagaag ucgucaagaa gaugaagaac	2640
uacuggagac agcugcugaa cgcaaagcug aucacacaga gaaaguucga caaccugaca	2700
aaggcagaga gaggaggacu gagcgaacug gacaaggcag gauucaucaa gagacagcug	2760
gucgaaacaa gacagaucaac aaagcagcuc gcacagaucc uggacagcag aaugaacaca	2820
aaguacgacg aaaacgacaa gcugaucaga gaagucaagg ucaucacacu gaagagcaag	2880
cuggucagcg acuucagaaa ggacuuccag uucuacaagg ucagagaaa caacaacuac	2940
caccacgcac acgacgcaua ccugaacgca gucgucggaa cagcacugau caagaaguac	3000
ccgaagcugg aaagcgauu cgucacgga gacuacaagg ucuacgacgu cagaaagaug	3060
aucgcaaaga gcgaacagga aaucggaaag gcaacagcaa aguacuucuu cuacagcaac	3120
aucaugaacu ucuucaagac agaaucaca cuggcaaacg gagaaucag aaagagaccg	3180

cugaucgaaa caaacggaga aacaggagaa aucgucuggg acaagggaag agacuucgca 3240
acagucagaa agguccugag caugccgcag gucaaucug ucaagaagac agaaguccag 3300
acaggaggau ucagcaagga aagcauccug ccgaagagaa acagcgacaa gcugaucgca 3360
agaaagaagg acugggaccc gaagaaguac ggaggauucg acagcccgac agucgcauac 3420
agcguccugg ucgucgcaaa ggucgaaaag ggaaagagca agaagcugaa gagcgucaag 3480
gaacugcugg gaucacaaau cauggaaaga agcagcuucg aaaagaaccc gaucgacuuc 3540
cuggaagcaa agggauacaa ggaagucaag aaggaccuga ucaucaagcu gccgaaguac 3600
agccuguucg aacugggaaa cggaagaaag agaaugcugg caagcgagg agaacugcag 3660
aagggaacg aacuggcacu gccgagcaag uacgucaacu uccuguaccu ggcaagccac 3720
uacgaaaagc ugaagggaag cccggaagac aacgaacaga agcagcuguu cgucgaacag 3780
cacaagcacu accuggacga aaucaucgaa cagaucagcg aaucagcaa gagagucauc 3840
cuggcagacg caaaccugga caagguccug agcgcauaca acaagcacag agacaagccg 3900
aucagagaac aggcagaaaa caucauccac cuguucacac ugacaaaccu gggagcaccg 3960
gcagcauua aguacuucga cacaacauc gacagaaaga gauacacaag cacaaggaa 4020
guccuggacg caacacugau ccaccagagc aucacaggac uguacgaaac aagaaucgac 4080
cugagccagc ugaggaggaga c 4101

<210> 219
<211> 1368
<212> PRT
<213> Secuencia artificial

<220>
<223> Sintético: secuencia de aminoácidos de dCas9 (sin NLS)

<400> 219

Met Asp Lys Lys Tyr Ser Ile Gly Leu Ala Ile Gly Thr Asn Ser Val
1 5 10 15

Gly Trp Ala Val Ile Thr Asp Glu Tyr Lys Val Pro Ser Lys Lys Phe
20 25 30

Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys Lys Asn Leu Ile
35 40 45

Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu
50 55 60

Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys
65 70 75 80

Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met Ala Lys Val Asp Asp Ser
 85 90 95

Phe Phe His Arg Leu Glu Glu Ser Phe Leu Val Glu Glu Asp Lys Lys
 100 105 110

His Glu Arg His Pro Ile Phe Gly Asn Ile Val Asp Glu Val Ala Tyr
 115 120 125

His Glu Lys Tyr Pro Thr Ile Tyr His Leu Arg Lys Lys Leu Val Asp
 130 135 140

Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile Tyr Leu Ala Leu Ala His
145 150 155 160

Met Ile Lys Phe Arg Gly His Phe Leu Ile Glu Gly Asp Leu Asn Pro
 165 170 175

Asp Asn Ser Asp Val Asp Lys Leu Phe Ile Gln Leu Val Gln Thr Tyr
 180 185 190

Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn Ala Ser Gly Val Asp Ala
 195 200 205

Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys Ser Arg Arg Leu Glu Asn
 210 215 220

Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys Asn Gly Leu Phe Gly Asn
225 230 235 240

Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro Asn Phe Lys Ser Asn Phe
 245 250 255

Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu Ser Lys Asp Thr Tyr Asp
 260 265 270

Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile Gly Asp Gln Tyr Ala Asp
 275 280 285

Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp Ala Ile Leu Leu Ser Asp
 290 295 300

Ile Leu Arg Val Asn Thr Glu Ile Thr Lys Ala Pro Leu Ser Ala Ser
305 310 315 320

Met Ile Lys Arg Tyr Asp Glu His His Gln Asp Leu Thr Leu Leu Lys
 325 330 335

Ala Leu Val Arg Gln Gln Leu Pro Glu Lys Tyr Lys Glu Ile Phe Phe
 340 345 350

Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr Ile Asp Gly Gly Ala Ser
 355 360 365

Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro Ile Leu Glu Lys Met Asp
 370 375 380

Gly Thr Glu Glu Leu Leu Val Lys Leu Asn Arg Glu Asp Leu Leu Arg
385 390 395 400

Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile Pro His Gln Ile His Leu
 405 410 415

Gly Glu Leu His Ala Ile Leu Arg Arg Gln Glu Asp Phe Tyr Pro Phe
 420 425 430

Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile
 435 440 445

Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp
 450 455 460

Met Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu
465 470 475 480

Val Val Asp Lys Gly Ala Ser Ala Gln Ser Phe Ile Glu Arg Met Thr
 485 490 495

Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys Val Leu Pro Lys His Ser
 500 505 510

Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu Leu Thr Lys Val Lys
 515 520 525

Tyr Val Thr Glu Gly Met Arg Lys Pro Ala Phe Leu Ser Gly Glu Gln

530	535	540
Lys Lys Ala Ile Val Asp Leu Leu Phe Lys Thr Asn Arg Lys Val Thr		
545	550	555 560
Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp		
565	570	575
Ser Val Glu Ile Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu Gly		
580	585	590
Thr Tyr His Asp Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp		
595	600	605
Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile Val Leu Thr Leu Thr		
610	615	620
Leu Phe Glu Asp Arg Glu Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala		
625	630	635 640
His Leu Phe Asp Asp Lys Val Met Lys Gln Leu Lys Arg Arg Arg Tyr		
645	650	655
Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp		
660	665	670
Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe		
675	680	685
Ala Asn Arg Asn Phe Met Gln Leu Ile His Asp Asp Ser Leu Thr Phe		
690	695	700
Lys Glu Asp Ile Gln Lys Ala Gln Val Ser Gly Gln Gly Asp Ser Leu		
705	710	715 720
His Glu His Ile Ala Asn Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly		
725	730	735
Ile Leu Gln Thr Val Lys Val Val Asp Glu Leu Val Lys Val Met Gly		
740	745	750
Arg His Lys Pro Glu Asn Ile Val Ile Glu Met Ala Arg Glu Asn Gln		
755	760	765

Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu Arg Met Lys Arg Ile
770 775 780

Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile Leu Lys Glu His Pro
785 790 795 800

Val Glu Asn Thr Gln Leu Gln Asn Glu Lys Leu Tyr Leu Tyr Tyr Leu
805 810 815

Gln Asn Gly Arg Asp Met Tyr Val Asp Gln Glu Leu Asp Ile Asn Arg
820 825 830

Leu Ser Asp Tyr Asp Val Asp Ala Ile Val Pro Gln Ser Phe Leu Lys
835 840 845

Asp Asp Ser Ile Asp Asn Lys Val Leu Thr Arg Ser Asp Lys Asn Arg
850 855 860

Gly Lys Ser Asp Asn Val Pro Ser Glu Glu Val Val Lys Lys Met Lys
865 870 875 880

Asn Tyr Trp Arg Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys
885 890 895

Phe Asp Asn Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp
900 905 910

Lys Ala Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr
915 920 925

Lys His Val Ala Gln Ile Leu Asp Ser Arg Met Asn Thr Lys Tyr Asp
930 935 940

Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys Ser
945 950 955 960

Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys Val Arg
965 970 975

Glu Ile Asn Asn Tyr His His Ala His Asp Ala Tyr Leu Asn Ala Val
980 985 990

Val Gly Thr Ala Leu Ile Lys Lys Tyr Pro Lys Leu Glu Ser Glu Phe
995 1000 1005

Val Tyr Gly Asp Tyr Lys Val Tyr Asp Val Arg Lys Met Ile Ala
1010 1015 1020

Lys Ser Glu Gln Glu Ile Gly Lys Ala Thr Ala Lys Tyr Phe Phe
1025 1030 1035

Tyr Ser Asn Ile Met Asn Phe Phe Lys Thr Glu Ile Thr Leu Ala
1040 1045 1050

Asn Gly Glu Ile Arg Lys Arg Pro Leu Ile Glu Thr Asn Gly Glu
1055 1060 1065

Thr Gly Glu Ile Val Trp Asp Lys Gly Arg Asp Phe Ala Thr Val
1070 1075 1080

Arg Lys Val Leu Ser Met Pro Gln Val Asn Ile Val Lys Lys Thr
1085 1090 1095

Glu Val Gln Thr Gly Gly Phe Ser Lys Glu Ser Ile Leu Pro Lys
1100 1105 1110

Arg Asn Ser Asp Lys Leu Ile Ala Arg Lys Lys Asp Trp Asp Pro
1115 1120 1125

Lys Lys Tyr Gly Gly Phe Asp Ser Pro Thr Val Ala Tyr Ser Val
1130 1135 1140

Leu Val Val Ala Lys Val Glu Lys Gly Lys Ser Lys Lys Leu Lys
1145 1150 1155

Ser Val Lys Glu Leu Leu Gly Ile Thr Ile Met Glu Arg Ser Ser
1160 1165 1170

Phe Glu Lys Asn Pro Ile Asp Phe Leu Glu Ala Lys Gly Tyr Lys
1175 1180 1185

Glu Val Lys Lys Asp Leu Ile Ile Lys Leu Pro Lys Tyr Ser Leu
1190 1195 1200

Phe Glu Leu Glu Asn Gly Arg Lys Arg Met Leu Ala Ser Ala Gly
1205 1210 1215

Glu Leu Gln Lys Gly Asn Glu Leu Ala Leu Pro Ser Lys Tyr Val
1220 1225 1230

Asn Phe Leu Tyr Leu Ala Ser His Tyr Glu Lys Leu Lys Gly Ser
1235 1240 1245

Pro Glu Asp Asn Glu Gln Lys Gln Leu Phe Val Glu Gln His Lys
1250 1255 1260

His Tyr Leu Asp Glu Ile Ile Glu Gln Ile Ser Glu Phe Ser Lys
1265 1270 1275

Arg Val Ile Leu Ala Asp Ala Asn Leu Asp Lys Val Leu Ser Ala
1280 1285 1290

Tyr Asn Lys His Arg Asp Lys Pro Ile Arg Glu Gln Ala Glu Asn
1295 1300 1305

Ile Ile His Leu Phe Thr Leu Thr Asn Leu Gly Ala Pro Ala Ala
1310 1315 1320

Phe Lys Tyr Phe Asp Thr Thr Ile Asp Arg Lys Arg Tyr Thr Ser
1325 1330 1335

Thr Lys Glu Val Leu Asp Ala Thr Leu Ile His Gln Ser Ile Thr
1340 1345 1350

Gly Leu Tyr Glu Thr Arg Ile Asp Leu Ser Gln Leu Gly Gly Asp
1355 1360 1365

<210> 220

<211> 4107

<212> ARN

<213> Secuencia artificial

<220>

<223> Sintético: ORF del ARNm de dCas9 que codifica la SEQ ID NO: 219 que usa codones de mínima uridina como se enumeran en la Tabla 3, con codones de inicio y parada

<400> 220

auggacaaga aguacagcau cggacuggca aucggaacaa acagcgucgg augggcaguc 60

aucacagacg aauacaaggu cccgagcaag aaguucaagg uccugggaaa cacagacaga 120

cacagcauca agaagaaccu gaucggagca cugcuguucg acagcggaga aacagcagaa 180

gcaacaagac ugaagagaac agcaagaaga agauacacaa gaagaaagaa cagaaucugc 240

uaccugcagg aaaucuucag caacgaaaug gcaaaggucg acgacagcuu cuuccacaga 300

cuggaagaaa gcuuccuggu cgaagaagac aagaagcacg aaagacaccc gaucuucgga 360

aacaucgucg acgaagucgc auaccacgaa aaguacccga caaucuacca ccugagaaaag	420
aagcuggucg acagcacaga caaggcagac cugagacuga ucuaccuggc acuggcacac	480
augaucaagu ucagaggaca cuuccugauc gaaggagacc ugaacccgga caacagcgac	540
gucgacaagc uguucaucca gcugguccag acauacaacc agcuguucga agaaaacccg	600
aucaacgcaa gcggagucga cgcaaaggca auccugagcg caagacugag caagagcaga	660
agacuggaaa accugaucgc acagcugccg ggagaaaaga agaacggacu guucggaaac	720
cugaucgcac ugagccuggg acugacaccg aacuuaaga gcaacuucga ccuggcagaa	780
gacgcaaagc ugcagcugag caaggacaca uacgacgacg accuggacaa ccugcuggca	840
cagaucggag accaguacgc agaccuguuc cuggcagcaa agaaccugag cgacgcauc	900
cugcugagcg acauccugag agucaacaca gaaucacaa aggcaccgcu gagcgcaagc	960
augaucaaga gauacgacga acaccaccag gaccugacac ugcugaaggc acuggucaga	1020
cagcagcugc cggaaaagua caaggaaauc uucuucgacc agagcaagaa cggauacgca	1080
ggauacaucg acggaggagc aagccaggaa gaauucuaca aguucauca gccgauccug	1140
gaaaagaugg acggaacaga agaacugcug gucaagcuga acagagaaga ccugcugaga	1200
aagcagagaa cauucgacaa cggaagcauc ccgcaccaga uccaccuggg agaacugcac	1260
gcaauccuga gaagacagga agacuucuac ccguuccuga aggacaacag agaaaagauc	1320
gaaaagaucc ugacauucag aaucccgua uacgucggac cgcuggcaag aggaaacagc	1380
agauucgcau ggauagacaag aaagagcgaa gaaacaauc caccugggaa cuucgaagaa	1440
gucgucgaca agggagcaag cgcacagagc uucaucgaaa gaaugacaaa cuucgacaag	1500
aaccugccga acgaaaaggu ccugccgaag cacagccugc uguacgaaua cuucacaguc	1560
uacaacgaac ugacaaaggu caaguacguc acagaaggaa ugagaaagcc ggcauuccug	1620
agcggagaac agaagaaggc aaucgucgac cugcuguuca agacaaacag aaaggucaca	1680
gucaagcagc ugaaggaaga cuacuuaag aagaucgaau gcuucgacag cgucgaaauc	1740
agcggagucg aagacagauu caacgcaagc cugggaacau accacgaccu gcugaagauc	1800
aucaaggaca aggacuuccu ggacaacgaa gaaaacgaag acauccugga agaucguc	1860
cugacacuga cacuguucga agacagagaa augaucgaag aaagacugaa gacauacgca	1920
caccuguucg acgacaaggu caugaagcag cugaagagaa gaagauacac aggaugggga	1980
agacugagca gaaagcugau caacggaauc agagacaagc agagcggaaa gacaauccug	2040
gacuuccuga agagcgacgg auucgcaaac agaaacuua ugcagcugau ccacgacgac	2100

agccugacau ucaaggaaga cauccagaag gcacagguca gcggacaggg agacagccug	2160
cacgaacaca ucgcaaaccu ggaggaagc ccggcaauca agaagggaau ccugcagaca	2220
gucaaggucg ucgacgaacu ggucaagguc augggaagac acaagccgga aaacaucguc	2280
aucgaaaugg caagagaaaa ccagacaaca cagaagggac agaagaacag cagagaaaga	2340
augaagagaa ucgaagaagg aaucaggaa cugggaagcc agauccugaa ggaacacccg	2400
gucgaaaaca cacagcugca gaacgaaaag cuguaccugu acuaccugca gaacggaaga	2460
gacauguacg ucgaccagga acuggacauc aacagacuga gcgacuacga cgucgacgca	2520
aucguccgc agagcuuccu gaaggacgac agcaucgaca acaagguccu gacaagaagc	2580
gacaagaaca gaggaagag cgacaacguc ccgagcgaag aagucgucaa gaagaugaag	2640
aacuacugga gacagcugcu gaacgcaaag cugaucacac agagaaaguu cgacaaccug	2700
acaaaggcag agagaggagg acugagcgaa cuggacaagg caggauucau caagagacag	2760
cuggucgaaa caagacagau cacaagcac gucgcacaga uccuggacag cagaaugaac	2820
acaaaguacg acgaaaacga caagcugauc agagaaguca aggucaucac acugaagagc	2880
aagcugguca gcgacuucag aaaggacuuc caguucuaca agguagaga aaucacaac	2940
uaccaccacg cacacgacgc auaccugaac gcagucgucg gaacagcacu gaucaagaag	3000
uaccgaagc uggaagcga auucgucuac ggagacuaca agguacuaga cgucagaaag	3060
augaucgaa agagcgaaca ggaaucgga aaggcaacag caaguacuu cuucuacagc	3120
aacauauga acuucuuaa gacagaaauc acacuggcaa acggagaaau cagaaagaga	3180
ccgcugaucg aaacaaacgg agaaacagga gaaucgucu gggacaaggg aagagacuuc	3240
gcaacaguca gaaagguccu gagcaugccg cagguaaca ucgucaagaa gacagaaguc	3300
cagacaggag gauucagcaa ggaaagcauc cugccgaaga gaaacagcga caagcugauc	3360
gcaagaaaga aggacuggga cccgaagaag uacggaggau ucgacagccc gacagucgca	3420
uacagcgucc ugguugucgc aaaggucgaa aagggaaga gcaagaagcu gaagagcugc	3480
aaggaacugc uggaauacac aaucaggaa agaagcagcu ucgaaaagaa cccgaucgac	3540
uuccuggaag caaagggaau caaggaaguc aagaaggacc ugaucauaa gcugccgaag	3600
uacagccugu ucgaacugga aaacggaaga aagagaagc uggaagcgc aggagaacug	3660
cagaaggga acgaacuggc acugccgagc aaguacguca acuuccugua ccuggcaagc	3720
cacuacgaaa agcugaaggg aagcccgaa gacaacgaac agaagcagcu guucgucgaa	3780
cagcacaagc acuaccugga cgaaucauc gaacagauca gcgaauucag caagagaguc	3840
auccggcag acgcaaaccu ggacaagguc cugagcgau acaacaagca cagagacaag	3900

ccgaucagag aacaggcaga aaacaucauc caccuguuca cacugacaaa ccugggagca	3960
ccggcagcau ucaaguacuu cgacacaaca aucgacagaa agagauacac aagcacaaag	4020
gaaguccugg acgcaacacu gauccaccag agcaucacag gacuguacga aacaagaau	4080
gaccugagcc agcuggggagg agacuag	4107

<210> 221
 <211> 4113
 <212> ARN
 <213> Secuencia artificial

<220>
 <223> Sintético: secuencia de codificación de dCas9 que codifica la SEQ ID NO: 219 que usa codones de mínima uridina como se enumeran en la Tabla 3 (sin codones de inicio o parada; adecuada para su inclusión en la secuencia de codificación de proteínas de fusión)

<400> 221	
gacaagaagu acagcaucgg acuggcaauc ggaacaaaca gcgucggaug ggcagucauc	60
acagacgaau acaagguccc gagcaagaag uucaaggucc ugggaaacac agacagacac	120
agcaucaaga agaaccugau cggagcacug cuguucgaca gcggagaaac agcagaagca	180
acaagacuga agagaacagc aagaagaaga uacacaagaa gaaagaacag aaucugcuac	240
cugcaggaaa ucuucagcaa cgaaauggca aaggucgacg acagcuucuu ccacagacug	300
gaagaaagcu uccuggucga agaagacaag aagcacgaaa gacacccgau cuucggaaac	360
aucgucgacg aagucgcaua ccacgaaaag uacccgacaa ucuaccaccu gagaagaag	420
cuggucgaca gcacagacaa ggcagaccug agacugaucu accuggcacu ggcacacaug	480
aucaaguuca gaggacacuu ccugaucgaa ggagaccuga acccgacaa cagcgacguc	540
gacaagcugu ucauccagcu gguccagaca uacaaccagc uguucgaaga aaacccgauc	600
aacgcaagcg gagucgacgc aaaggcauc cugagcgcaa gacugagcaa gagcagaaga	660
cuggaaaacc ugauvcgaca gcugccggga gaaaagaaga acggacuguu cggaaccug	720
aucgcacuga gccugggacu gacaccgaac uucaagagca acuucgaccu ggcagaagac	780
gcaaagcugc agcugagcaa ggacacauac gacgacgacc uggacaaccu gcuggcacag	840
aucggagacc aguacgcaga ccuguuccug gcagcaaaga accugagcga cgcaauccug	900
cugagcgaca uccugagagu caacacagaa aucacaaagg caccgcugag cgcaagcaug	960
aucaagagau acgacgaaca ccaccaggac cugacacugc ugaaggcacu ggucagacag	1020
cagcugccgg aaaaguacaa ggaaauuc uucgaccaga gcaagaacgg auacgcagga	1080
uauvcgacg gaggagcaag ccaggaagaa uucuacaagu ucaucaagcc gauccuggaa	1140

aagauggacg gaacagaaga acugcugguc aagcugaaca gagaagaccu gcugagaaag 1200
cagagaacau ucgacaacgg aagcaucccg caccagaucc accugggaga acugcacgca 1260
auccugagaa gacaggaaga cuucuacccg uuccugaagg acaacagaga aaagaucgaa 1320
aagauccuga cauucagaau cccguacuac gucggaccgc uggcaagagg aaacagcaga 1380
uucgcaugga ugacaagaaa gagcgaagaa acaaucacac cguggaacuu cgaagaaguc 1440
gucgacaagg gagcaagcgc acagagcuuc aucgaaagaa ugacaaacuu cgacaagaac 1500
cugccgaacg aaaagguccu gccgaagcac agccugcugu acgaauacuu cacagucuac 1560
aacgaacuga caaaggucaa guacgucaca gaaggaauga gaaagccggc auuccugagc 1620
ggagaacaga agaaggcaau cgucgaccug cuguucaaga caaacagaaa ggucacaguc 1680
aagcagcuga aggaagacua cuucaagaag aucgaaugcu ucgacagcgu cgaaaucagc 1740
ggagucgaag acagauucaa cgcaagccug ggaacauacc acgaccugcu gaagaucauc 1800
aaggacaagg acuuccugga caacgaagaa aacgaagaca uccuggaaga caucguccug 1860
acacugacac uguucgaaga cagagaaaug aucgaagaaa gacugaagac auacgcacac 1920
cuguucgacg acaaggucan gaagcagcug aagagaagaa gauacacagg auggggaaga 1980
cugagcagaa agcugaucaa cggaaucaaga gacaagcaga gcggaagac aauccuggac 2040
uuccugaaga gcgacggauu cgcaaacaga aacuucaugc agcugaucca cgacgacagc 2100
cugacauuca aggaagacau ccagaaggca caggucagcg gacagggaga cagccugcac 2160
gaacacaucg caaaccuggc aggaagcccg gcaaucaaga agggaauccu gcagacaguc 2220
aaggucgucg acgaacuggu caagguaug ggaagacaca agccggaaaa caucgucauc 2280
gaaauggcaa gagaaaacca gacaacacag aaggacaga agaacagcag agaaagaug 2340
aagagaaucg aagaaggaaau caaggaacug ggaagccaga uccugaagga acacccgguc 2400
gaaaacacac agcugcagaa cgaaaagcug uaccuguacu accugcagaa cggaagagac 2460
auguacgucg accaggaacu ggacaucaac agacugagcg acuacgacgu cgacgcauc 2520
guccgcaga gcuuccugaa ggacgacagc aucgacaaca agguccugac aagaagcgac 2580
aagaacagag gaaagagcga caacgucccg agcgaagaag ucgucaagaa gaugaagaac 2640
uacuggagac agcugcugaa cgcaaagcug aucacacaga gaaaguucga caaccugaca 2700
aaggcagaga gaggaggacu gagcgaacug gacaaggcag gauucaucaa gagacagcug 2760
gucgaaacaa gacagaucac aaagcacguc gcacagaucc uggacagcag aaugaacaca 2820
aaguacgacg aaaacgacaa gcugaucaga gaagucaagg ucaucacacu gaagagcaag 2880
cuggucagcg acuucagaaa ggacuuccag uucuacaagg ucagagaaau caacaacuac 2940

caccacgcac acgacgcgcau ccugaacgca gucgucggaa cagcacugau caagaaguac	3000
ccgaagcugg aaagcgaaau cgucuacgga gacuacaagg ucuacgacgu cagaaagaug	3060
aucgcaaaga gcgaacagga aaucggaaa gcaacagcaa aguacuucuu cuacagcaac	3120
aucaugaacu ucuucaagac agaaaucaca cuggcaaacg gagaaaucag aaagagaccg	3180
cugaucgaaa caaacggaga aacaggagaa aucgucuggg acaagggaag agacuucgca	3240
acagucagaa agguccugag caugccgcag gucaacaucg ucaagaagac agaaguccag	3300
acaggaggau ucagcaagga aagcauccug ccgaagagaa acagcgacaa gcugaucgca	3360
agaaagaagg acugggaccc gaagaaguac ggaggauucg acagcccgcag agucgcgauac	3420
agcguccugg ucgucgcaaa ggucgaaaa ggaaagagca agaagcugaa gagcgucaag	3480
gaacugcugg gaaucacaau cauggaaaga agcagcuucg aaaagaaccc gaucgacuuc	3540
cuggaagcaa agggauacaa ggaagucaag aaggaccuga ucaucaagcu gccgaaguac	3600
agccuguucg aacugggaaa cggaagaaag agaauvcugg caagcgagg agaacugcag	3660
aagggaaacg aacuggcacu gccgagcaag uacgucaacu uccuguaccu ggcaagccac	3720
uacgaaaagc ugaagggaag cccggaagac aacgaacaga agcagcuguu cgucgaacag	3780
cacaagcacu accuggacga aaucaucgaa cagaucagcg aaucagcaa gagagucauc	3840
cuggcagacg caaaccugga caagguccug agcgcauaca acaagcacag agacaagccg	3900
aucagagaac aggcagaaaa caucauccac cuguucacac ugacaaaccu gggagcaccg	3960
gcagcauua aguacuucga cacaacauc gacagaaaga gauacacaag cacaaaggaa	4020
guccuggacg caacacugau ccaccagagc aucacaggac uguacgaaac aagaaucgac	4080
cugagccagc ugaggaggaga cggaggagga agc	4113

Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys Lys Asn Leu Ile
35 40 45

Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu
50 55 60

Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys
65 70 75 80

Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met Ala Lys Val Asp Asp Ser
85 90 95

Phe Phe His Arg Leu Glu Glu Ser Phe Leu Val Glu Glu Asp Lys Lys
100 105 110

His Glu Arg His Pro Ile Phe Gly Asn Ile Val Asp Glu Val Ala Tyr
115 120 125

His Glu Lys Tyr Pro Thr Ile Tyr His Leu Arg Lys Lys Leu Val Asp
130 135 140

Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile Tyr Leu Ala Leu Ala His
145 150 155 160

Met Ile Lys Phe Arg Gly His Phe Leu Ile Glu Gly Asp Leu Asn Pro
165 170 175

Asp Asn Ser Asp Val Asp Lys Leu Phe Ile Gln Leu Val Gln Thr Tyr
180 185 190

Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn Ala Ser Gly Val Asp Ala
195 200 205

Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys Ser Arg Arg Leu Glu Asn
210 215 220

Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys Asn Gly Leu Phe Gly Asn
225 230 235 240

Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro Asn Phe Lys Ser Asn Phe
245 250 255

Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu Ser Lys Asp Thr Tyr Asp

260	265	270
Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile Gly Asp Gln Tyr Ala Asp		
275	280	285
Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp Ala Ile Leu Leu Ser Asp		
290	295	300
Ile Leu Arg Val Asn Thr Glu Ile Thr Lys Ala Pro Leu Ser Ala Ser		
305	310	315 320
Met Ile Lys Arg Tyr Asp Glu His His Gln Asp Leu Thr Leu Leu Lys		
325	330	335
Ala Leu Val Arg Gln Gln Leu Pro Glu Lys Tyr Lys Glu Ile Phe Phe		
340	345	350
Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr Ile Asp Gly Gly Ala Ser		
355	360	365
Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro Ile Leu Glu Lys Met Asp		
370	375	380
Gly Thr Glu Glu Leu Leu Val Lys Leu Asn Arg Glu Asp Leu Leu Arg		
385	390	395 400
Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile Pro His Gln Ile His Leu		
405	410	415
Gly Glu Leu His Ala Ile Leu Arg Arg Gln Glu Asp Phe Tyr Pro Phe		
420	425	430
Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile		
435	440	445
Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp		
450	455	460
Met Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu		
465	470	475 480
Val Val Asp Lys Gly Ala Ser Ala Gln Ser Phe Ile Glu Arg Met Thr		
485	490	495

Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys Val Leu Pro Lys His Ser
500 505 510

Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu Leu Thr Lys Val Lys
515 520 525

Tyr Val Thr Glu Gly Met Arg Lys Pro Ala Phe Leu Ser Gly Glu Gln
530 535 540

Lys Lys Ala Ile Val Asp Leu Leu Phe Lys Thr Asn Arg Lys Val Thr
545 550 555 560

Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp
565 570 575

Ser Val Glu Ile Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu Gly
580 585 590

Thr Tyr His Asp Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp
595 600 605

Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile Val Leu Thr Leu Thr
610 615 620

Leu Phe Glu Asp Arg Glu Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala
625 630 635 640

His Leu Phe Asp Asp Lys Val Met Lys Gln Leu Lys Arg Arg Arg Tyr
645 650 655

Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp
660 665 670

Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe
675 680 685

Ala Asn Arg Asn Phe Met Gln Leu Ile His Asp Asp Ser Leu Thr Phe
690 695 700

Lys Glu Asp Ile Gln Lys Ala Gln Val Ser Gly Gln Gly Asp Ser Leu
705 710 715 720

His Glu His Ile Ala Asn Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly
725 730 735

Ile Leu Gln Thr Val Lys Val Val Asp Glu Leu Val Lys Val Met Gly
740 745 750

Arg His Lys Pro Glu Asn Ile Val Ile Glu Met Ala Arg Glu Asn Gln
755 760 765

Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu Arg Met Lys Arg Ile
770 775 780

Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile Leu Lys Glu His Pro
785 790 795 800

Val Glu Asn Thr Gln Leu Gln Asn Glu Lys Leu Tyr Leu Tyr Tyr Leu
805 810 815

Gln Asn Gly Arg Asp Met Tyr Val Asp Gln Glu Leu Asp Ile Asn Arg
820 825 830

Leu Ser Asp Tyr Asp Val Asp His Ile Val Pro Gln Ser Phe Leu Lys
835 840 845

Asp Asp Ser Ile Asp Asn Lys Val Leu Thr Arg Ser Asp Lys Asn Arg
850 855 860

Gly Lys Ser Asp Asn Val Pro Ser Glu Glu Val Val Lys Lys Met Lys
865 870 875 880

Asn Tyr Trp Arg Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys
885 890 895

Phe Asp Asn Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp
900 905 910

Lys Ala Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr
915 920 925

Lys His Val Ala Gln Ile Leu Asp Ser Arg Met Asn Thr Lys Tyr Asp
930 935 940

Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys Ser
945 950 955 960

Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys Val Arg
965 970 975

Glu Ile Asn Asn Tyr His His Ala His Asp Ala Tyr Leu Asn Ala Val
980 985 990

Val Gly Thr Ala Leu Ile Lys Lys Tyr Pro Lys Leu Glu Ser Glu Phe
995 1000 1005

Val Tyr Gly Asp Tyr Lys Val Tyr Asp Val Arg Lys Met Ile Ala
1010 1015 1020

Lys Ser Glu Gln Glu Ile Gly Lys Ala Thr Ala Lys Tyr Phe Phe
1025 1030 1035

Tyr Ser Asn Ile Met Asn Phe Phe Lys Thr Glu Ile Thr Leu Ala
1040 1045 1050

Asn Gly Glu Ile Arg Lys Arg Pro Leu Ile Glu Thr Asn Gly Glu
1055 1060 1065

Thr Gly Glu Ile Val Trp Asp Lys Gly Arg Asp Phe Ala Thr Val
1070 1075 1080

Arg Lys Val Leu Ser Met Pro Gln Val Asn Ile Val Lys Lys Thr
1085 1090 1095

Glu Val Gln Thr Gly Gly Phe Ser Lys Glu Ser Ile Leu Pro Lys
1100 1105 1110

Arg Asn Ser Asp Lys Leu Ile Ala Arg Lys Lys Asp Trp Asp Pro
1115 1120 1125

Lys Lys Tyr Gly Gly Phe Asp Ser Pro Thr Val Ala Tyr Ser Val
1130 1135 1140

Leu Val Val Ala Lys Val Glu Lys Gly Lys Ser Lys Lys Leu Lys
1145 1150 1155

Ser Val Lys Glu Leu Leu Gly Ile Thr Ile Met Glu Arg Ser Ser
1160 1165 1170

Phe Glu Lys Asn Pro Ile Asp Phe Leu Glu Ala Lys Gly Tyr Lys
1175 1180 1185

Glu Val Lys Lys Asp Leu Ile Ile Lys Leu Pro Lys Tyr Ser Leu

1190	1195	1200
Phe Glu	Leu Glu Asn Gly Arg	Lys Arg Met Leu Ala Ser Ala Gly
1205	1210	1215
Glu Leu	Gln Lys Gly Asn Glu	Leu Ala Leu Pro Ser Lys Tyr Val
1220	1225	1230
Asn Phe	Leu Tyr Leu Ala Ser	His Tyr Glu Lys Leu Lys Gly Ser
1235	1240	1245
Pro Glu	Asp Asn Glu Gln Lys	Gln Leu Phe Val Glu Gln His Lys
1250	1255	1260
His Tyr	Leu Asp Glu Ile Ile	Glu Gln Ile Ser Glu Phe Ser Lys
1265	1270	1275
Arg Val	Ile Leu Ala Asp Ala	Asn Leu Asp Lys Val Leu Ser Ala
1280	1285	1290
Tyr Asn	Lys His Arg Asp Lys	Pro Ile Arg Glu Gln Ala Glu Asn
1295	1300	1305
Ile Ile	His Leu Phe Thr Leu	Thr Asn Leu Gly Ala Pro Ala Ala
1310	1315	1320
Phe Lys	Tyr Phe Asp Thr Thr	Ile Asp Arg Lys Arg Tyr Thr Ser
1325	1330	1335
Thr Lys	Glu Val Leu Asp Ala	Thr Leu Ile His Gln Ser Ile Thr
1340	1345	1350
Gly Leu	Tyr Glu Thr Arg Ile	Asp Leu Ser Gln Leu Gly Gly Asp
1355	1360	1365
Gly Ser	Gly Ser Pro Lys Lys	Lys Arg Lys Val Asp Gly Ser Pro
1370	1375	1380
Lys Lys	Lys Arg Lys Val Asp	Ser Gly
1385	1390	

<210> 223
 <211> 4233
 <212> ARN
 <213> Secuencia artificial

<220>

<223> Sintético: ORF del ARNm de Cas9 que codifica la SEQ ID NO: 222 que usa codones de mínima uridina, con codones de inicio y parada

<400> 223

auggacaaga aguacagcau cggacuggac aucggaacaa acagcgucgg augggcaguc	60
aucacagacg aauacaaggu cccgagcaag aaguucaagg uccugggaaa cacagacaga	120
cacagcauca agaagaaccu gaucggagca cugcuguucg acagcggaga aacagcagaa	180
gcaacaagac ugaagagaac agcaagaaga agauacacaa gaagaaagaa cagaauucg	240
uaccugcagg aaaucuucag caacgaaaug gcaaaggucg acgacagcuu cuuccacaga	300
cuggaagaaa gcuuccuggu cgaagaagac aagaagcacg aaagacaccc gaucuucgga	360
aacaucgucg acgaagucgc auaccacgaa aaguacccga caaucuacca ccugagaaag	420
aagcuggucg acagcacaga caaggcagac cugagacuga ucuaccuggc acuggcacac	480
augaucaagu ucagaggaca cuuccugauc gaaggagacc ugaacccgga caacagcgac	540
gucgacaagc uguucaucca gcugguccag acauacaacc agcuguucga agaaaacccg	600
aucaacgcaa gcggagucga cgcaaaggca auccugagcg caagacugag caagagcaga	660
agacuggaaa accugaucgc acagcugccg ggagaaaaga agaacggacu guucggaaac	720
cugaucgcac ugagccuggg acugacaccg aacuucaaga gcaacuucga ccuggcagaa	780
gacgcaaagc ugcagcugag caaggacaca uacgacgacg accuggacaa ccugcuggca	840
cagaucggag accaguacgc agaccuguuc cuggcagcaa agaaccugag cgacgcauc	900
cugcugagcg acauccugag agucaacaca gaaucacaa aggcaccgcu gagcgcaagc	960
augaucaaga gauacgacga acaccaccag gaccugacac ugcugaaggc acuggucaga	1020
cagcagcugc cggaaaagua caaggaaauc uucuucgacc agagcaagaa cggauacgca	1080
ggauacaucg acggaggagc aagccaggaa gaauucuaca aguucauca gccgauccug	1140
gaaaagaugg acggaacaga agaacugcug gucaagcuga acagagaaga ccugcugaga	1200
aagcagagaa cauucgacaa cggaagcauc ccgcaccaga uccaccuggg agaacugcac	1260
gcaauccuga gaagacagga agacuucuac ccguuccuga aggacaacag agaaaagauc	1320
gaaaagaucc ugacauucag aaucccgua uacgucggac cgcuggcaag aggaaacagc	1380
agauucgcau ggaugacaag aaagagcgaa gaaacaauca caccugggaa cuucgaagaa	1440
gucgucgaca agggagcaag cgcacagagc uucaucgaaa gaaugacaaa cuucgacaag	1500
aaccugccga acgaaaaggu ccugccgaag cacagccugc uguacgaaua cuucacaguc	1560
uacaacgaac ugacaaaggu caaguacguc acagaaggaa ugagaaagcc ggcauuccug	1620

agcggagaac agaagaaggc aaucgucgac cugcuguuca agacaaacag aaaggucaca	1680
gucaagcagc ugaaggaaga cuacuucaag aagaucgaau gcuucgacag cgucgaaauc	1740
agcggagucg aagacagauu caacgcaagc cugggaacau accacgaccu gcugaagauc	1800
aucaaggaca aggacuuccu ggacaacgaa gaaaacgaag acauccugga agacaucguc	1860
cugacacuga cacuguucga agacagagaa augaucgaag aaagacugaa gacauacgca	1920
caccuguucg acgacaaggu caugaagcag cugaagagaa gaagauacac aggaugggga	1980
agacugagca gaaagcugau caacggaauc agagacaagc agagcggaaa gacaauccug	2040
gacuuccuga agagcgacgg auucgcaaac agaaacuuca ugcagcugau ccacgacgac	2100
agccugacau ucaaggaaga cauccagaag gcacagguca gcggacaggg agacagccug	2160
cacgaacaca ucgcaaaccu ggcaaggagc ccggcaauca agaagggaau ccugcagaca	2220
gucaaggucg ugcacgaacu ggucaagguc augggaagac acaagccgga aaacaucguc	2280
aucgaaaugg caagagaaaa ccagacaaca cagaagggac agaagaacag cagagaaaga	2340
augaagagaa ucgaagaagg aaucaggaa cugggaagcc agauccugaa ggaacacccg	2400
gucgaaaaca cacagcugca gaacgaaaag cuguaccugu acuaccugca gaacggaaga	2460
gacauguacg ugcaccagga acuggacauc aacagacuga gcgacuacga cgucgaccac	2520
aucguccgc agagcuuccu gaaggacgac agcaucgaca acaagguccu gacaagaagc	2580
gacaagaaca gaggaagag cgacaacguc ccgagcgaag aagucgucaa gaagaugaag	2640
aacuacugga gacagcugcu gaacgcaaag cugaucacac agagaaaguu cgacaaccug	2700
acaaaggcag agagaggagg acugagcgaa cuggacaagg caggauucau caagagacag	2760
cuggucgaaa caagacagau cacaagcac gucgcacaga uccuggacag cagaaugaac	2820
acaaaguacg acgaaaacga caagcugauc agagaaguca aggucaucac acugaagagc	2880
aagcugguca gcgacuucag aaaggacuuc caguucuaca agguagaga aaucacaac	2940
uaccaccacg cacacgacgc auaccugaac gcagucgucg gaacagcacu gaucaagaag	3000
uaccgaagc uggaaagcga auucgucuac ggagacuaca agguacuaga cgucagaaag	3060
augaucgcaa agagcgaaca ggaaucgga aaggcaacag caaguacuu cuucuacagc	3120
aacaucauga acuucuucac gacagaaauc acacuggcaa acggagaaaau cagaaagaga	3180
ccgcugaucg aaacaaacgg agaaacagga gaaucgucu gggacaaggg aagagacuuc	3240
gcaacaguca gaaagguccu gagcaugccg cagguaaca ucgucaagaa gacagaaguc	3300
cagacaggag gauucagcaa ggaaagcauc cugccgaaga gaaacagcga caagcugauc	3360

gcaagaaaga aggacuggga cccgaagaag uacggaggau ucgacagccc gacagucgca	3420
uacagcgucc uggucgucgc aaaggucgaa aagggaaaga gcaagaagcu gaagagcguc	3480
aaggaacugc ugggaaucaac aaucauggaa agaagcagcu ucgaaaagaa cccgaucgac	3540
uuccuggaag caaagggaaua caaggaaguc aagaaggacc ugaucauca gcuGCCgaag	3600
uacagccugu ucgaacugga aaacggaaga aagagaauGC uggcaagcgc aggagaacug	3660
cagaagggaac acgaacuggc acugccgagc aaguacguca acuuccugua ccuggcaagc	3720
cacuacgaaa agcugaaggg aagcccggaa gacaacgaac agaagcagcu guucgucgaa	3780
cagcacaagc acuaccugga cgaaucauc gaacagauca gcgaauucag caagagaguc	3840
auccuggcag acgcaaaccu ggacaagguc cugagcgcau acaacaagca cagagacaag	3900
ccgaucagag aacaggcaga aaacaucauc caccuguuca cacugacaaa ccugggagca	3960
ccggcagcau ucaaguacuu cgacacaaca aucgacagaa agagauacac aagcacaag	4020
gaaguccugg acgcaacacu gauccaccag agcaucacag gacuguacga aacaagaauC	4080
gaccugagcc agcuggggagg agacggagga ggaagcccga agaagaagag aaaggucCCg	4140
aagaagaaga gaaaggucgg aagcggaagc ccgaagaaga agagaaaggu cgacggaagc	4200
ccgaagaaga agagaaaggu cgacagcgga uag	4233

<210> 224
 <211> 4227
 <212> ARN
 <213> Secuencia artificial

<220>
 <223> Sintético: secuencia de codificación de Cas9 que codifica la SEQ ID NO: 222 que usa codones de mínima uridina (sin codones de inicio y parada; adecuada para su inclusión en la secuencia de codificación de proteínas de fusión)

<400> 224	
gacaagaagu acagcaucgg acuggacauc ggaacaaaca gcgucggaug ggcagucauc	60
acagacgaau acaaggucCC gagcaagaag uucaaggucc ugggaaacac agacagacac	120
agcaucaaga agaaccugau cggagcacug cuguucgaca gcggagaaac agcagaagca	180
acaagacuga agagaacagc aagaagaaga uacacaagaa gaaagaacag aaucugcuac	240
cugcaggaaa ucuucagcaa cgaauggca aaggucgacg acagcuucuu ccacagacug	300
gaagaaagcu uccuggucga agaagacaag aagcacgaaa gacacCCgau cuucggaaac	360
aucgucgacg aagucgcaua ccacgaaaag uacCCgacaa ucuaccaccu gagaagaag	420
cuggucgaca gcacagacaa ggCagaccug agacugaucu accuggcacu ggcacacaug	480
aucaaguuca gaggacacuu ccgaucgaa ggagaccuga accCGgacaa cagcgacguc	540

gacaagcugu ucauccagcu gguccagaca uacaaccagc uguucgaaga aaacccgauc	600
aacgcaagcg gagucgacgc aaaggcaauc cugagcgcaa gacugagcaa gagcagaaga	660
cuggaaaacc ugau cgacaca gcugccggga gaaaagaaga acggacuguu cggaaccug	720
aucgcacuga gccugggacu gacaccgaac uucaagagca acuucgaccu ggcagaagac	780
gcaaagcugc agcugagcaa ggacacauac gacgacgacc uggacaaccu gcuggcacag	840
aucggagacc aguacgcaga ccuguuccug gcagcaaaga accugagcga cgcauccug	900
cugagcgaca uccugagagu caacacagaa aucacaaagg caccgcugag cgcaagcaug	960
aucaagagau acgacgaaca ccaccaggac cugacacugc ugaaggcacu ggucagacag	1020
cagcugccgg aaaaguacaa ggaaauuc uucgaccaga gcaagaacgg auacgcagga	1080
uauucgacg gaggagcaag ccaggaagaa uucuacaagu ucaucaagcc gauccuggaa	1140
aagauggacg gaacagaaga acugcugguc aagcugaaca gagaagaccu gcugagaaag	1200
cagagaacau ucgacaacgg aagcaucccg caccagauc accugggaga acugcacga	1260
auccugagaa gacaggaaga cuucuacccg uuccugaagg acaacagaga aaagaucgaa	1320
aagauccuga cauucagaau cccguacuac gucggaccgc uggcaagagg aaacagcaga	1380
uucgcaugga ugacaagaaa gagcgaagaa acauacacac cguggaacuu cgaagaaguc	1440
gucgacaagg gagcaagcg acagagcuuc aucgaaagaa ugacaaacuu cgacaagaac	1500
cugccgaacg aaaagguccu gccgaagcac agccugcugu acgaauacuu cacagucuac	1560
aacgaacuga caaaggucua guacgucaca gaaggaauga gaaagccggc auuccugagc	1620
ggagaacaga agaaggcaau cgucgaccug cuguucaaga caaacagaaa ggucacaguc	1680
aagcagcuga aggaagacua cuucaagaag aucgaaugcu ucgacagcgu cgaaucagc	1740
ggagucgaag acagauucaa cgcaagccug ggaacauacc acgaccugcu gaagaucauc	1800
aaggacaagg acuuccugga caacgaagaa aacgaagaca uccuggaaga caucguccug	1860
acacugacac uguucgaaga cagagaaaug aucgaagaaa gacugaagac auacgcacac	1920
cuguucgacg acaaggucua gaagcagcug aagagaagaa gauacacagg auggggaaga	1980
cugagcagaa agcugaucaa cggaucaga gacaagcaga gcggaagac aauccuggac	2040
uuccugaaga gcgacggauu cgaaacaga aacuucagc agcugaucca cgacgacagc	2100
cugacauuca aggaagacau ccagaaggca caggucagcg gacagggaga cagccugcac	2160
gaacacaucg caaaccuggc aggaagccc gcaaucaaga agggaaucuu gcagacaguc	2220
aaggucgucg acgaacuggu caagguaug ggaagacaca agccggaaaa caucgucauc	2280

gaaauggcaa gagaaaacca gacaacacag aaggacaga agaacagcag agaaagaug	2340
aagagaaucg aagaaggaa caaggaacug ggaagccaga uccugaagga acacccgguc	2400
gaaaacacac agcugcagaa cgaaaagcug uaccuguacu accugcagaa cggaagagac	2460
auguacgucg accaggaacu ggacaucaac agacugagcg acucgacgu cgaccacau	2520
guccgcaga gcuuccugaa ggacgacagc aucgacaaca agguccugac aagaagcgac	2580
aagaacagag gaaagagcga caacguccc agcgaagaag ucucaagaa gaugaagaac	2640
uacuggagac agcugcugaa cgaaaagcug aucacacaga gaaaguucga caaccugaca	2700
aaggcagaga gaggaggacu gagcgaacug gacaaggcag gauucauaa gagacagcug	2760
gucgaaaca gacagaucaac aaagcacguc gcacagaucc uggacagcag aaugaacaca	2820
aaguacgacg aaaacgaca gcugaucaga gaagucaagg ucaucacacu gaagagcaag	2880
cuggucagcg acuucagaaa ggacuuccag uucuacaagg ucagagaaa caacaacuac	2940
caccacgcac acgacgcau ccugaacgca gucgucggaa cagcacugau caagaaguac	3000
ccgaagcugg aaagcgaa ucuacgga gacuacaagg ucuacgacgu cagaaagaug	3060
aucgcaaaga gcgaacagga aaucggaaag gcaacagca aguacuucu cuacagcaac	3120
aucaugaacu ucucaagac agaaucaca cuggcaaagc gagaaucag aaagagaccg	3180
cugaucgaaa caaacggaga aacaggagaa aucgucggg acaagggaag agacuucgca	3240
acagucagaa agguccugag caugccgcag gucaaucaug ucaagaagac agaaguccag	3300
acaggaggau ucagcaagga aagcauccug ccgaagagaa acagcgaca gcugaucgca	3360
agaaagaagg acugggaccc gaagaaguac ggaggauucg acagcccgac agucgcauac	3420
agcguccugg ucgucgaaa ggucgaaaag ggaaagagca agaagcugaa gagcguaag	3480
gaacugcugg gaucacaau cauggaaaga agcagcuucg aaaagaacc gaucgacuuc	3540
cuggaagcaa agggauaca ggaagucaag aaggaccuga ucaucaagcu gccgaaguac	3600
agccguucg aacuggaaaa cggaagaaag agaauugcugg caagcgagg agaacugcag	3660
aagggaacg aacuggcacu gccgagcaag uacgucaacu uccuguaccu ggcaagccac	3720
uacgaaaagc ugaagggaag cccggaagac aacgaacaga agcagcuguu cgucgaacag	3780
cacaagcacu accuggacga aaucaucgaa cagaucagcg aaucagcaa gagagucauc	3840
cuggcagacg caaaccugga caagguccug agcgcauaca acaagcacag agacaagccg	3900
aucagagaac aggcagaaaa caucauccac cuguucacac ugacaaaccu gggagcaccg	3960
gcagcauua aguacuucga cacaacauc gacagaaaga gauacacaag cacaaggaa	4020
guccggacg caacacugau ccaccagagc aucacaggac uguacgaaac aagaucgac	4080

cugagccagc ugggaggaga cggaggagga agcccgaaga agaagagaaa ggucccgaag 4140
aagaagagaa aggucggaag cggaagcccg aagaagaaga gaaaggucga cggaagcccg 4200
aagaagaaga gaaaggucga cagcgga 4227

<210> 225
<211> 1392
<212> PRT
<213> Secuencia artificial

<220>
<223> Sintético: secuencia de aminoácidos de la nickasa Cas9 con dos señales de localización nuclear como los aminoácidos C-terminales

<400> 225

Met Asp Lys Lys Tyr Ser Ile Gly Leu Ala Ile Gly Thr Asn Ser Val
1 5 10 15

Gly Trp Ala Val Ile Thr Asp Glu Tyr Lys Val Pro Ser Lys Lys Phe
20 25 30

Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys Lys Asn Leu Ile
35 40 45

Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu
50 55 60

Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys
65 70 75 80

Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met Ala Lys Val Asp Asp Ser
85 90 95

Phe Phe His Arg Leu Glu Glu Ser Phe Leu Val Glu Glu Asp Lys Lys
100 105 110

His Glu Arg His Pro Ile Phe Gly Asn Ile Val Asp Glu Val Ala Tyr
115 120 125

His Glu Lys Tyr Pro Thr Ile Tyr His Leu Arg Lys Lys Leu Val Asp
130 135 140

Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile Tyr Leu Ala Leu Ala His
145 150 155 160

Met Ile Lys Phe Arg Gly His Phe Leu Ile Glu Gly Asp Leu Asn Pro
165 170 175

Asp Asn Ser Asp Val Asp Lys Leu Phe Ile Gln Leu Val Gln Thr Tyr
180 185 190

Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn Ala Ser Gly Val Asp Ala
195 200 205

Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys Ser Arg Arg Leu Glu Asn
210 215 220

Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys Asn Gly Leu Phe Gly Asn
225 230 235 240

Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro Asn Phe Lys Ser Asn Phe
245 250 255

Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu Ser Lys Asp Thr Tyr Asp
260 265 270

Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile Gly Asp Gln Tyr Ala Asp
275 280 285

Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp Ala Ile Leu Leu Ser Asp
290 295 300

Ile Leu Arg Val Asn Thr Glu Ile Thr Lys Ala Pro Leu Ser Ala Ser
305 310 315 320

Met Ile Lys Arg Tyr Asp Glu His His Gln Asp Leu Thr Leu Leu Lys
325 330 335

Ala Leu Val Arg Gln Gln Leu Pro Glu Lys Tyr Lys Glu Ile Phe Phe
340 345 350

Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr Ile Asp Gly Gly Ala Ser
355 360 365

Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro Ile Leu Glu Lys Met Asp
370 375 380

Gly Thr Glu Glu Leu Leu Val Lys Leu Asn Arg Glu Asp Leu Leu Arg
385 390 395 400

Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile Pro His Gln Ile His Leu
405 410 415

Gly Glu Leu His Ala Ile Leu Arg Arg Gln Glu Asp Phe Tyr Pro Phe
420 425 430

Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile
435 440 445

Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp
450 455 460

Met Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu
465 470 475 480

Val Val Asp Lys Gly Ala Ser Ala Gln Ser Phe Ile Glu Arg Met Thr
485 490 495

Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys Val Leu Pro Lys His Ser
500 505 510

Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu Leu Thr Lys Val Lys
515 520 525

Tyr Val Thr Glu Gly Met Arg Lys Pro Ala Phe Leu Ser Gly Glu Gln
530 535 540

Lys Lys Ala Ile Val Asp Leu Leu Phe Lys Thr Asn Arg Lys Val Thr
545 550 555 560

Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp
565 570 575

Ser Val Glu Ile Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu Gly
580 585 590

Thr Tyr His Asp Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp
595 600 605

Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile Val Leu Thr Leu Thr
610 615 620

Leu Phe Glu Asp Arg Glu Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala
625 630 635 640

His Leu Phe Asp Asp Lys Val Met Lys Gln Leu Lys Arg Arg Arg Tyr
645 650 655

Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp
660 665 670

Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe
675 680 685

Ala Asn Arg Asn Phe Met Gln Leu Ile His Asp Asp Ser Leu Thr Phe
690 695 700

Lys Glu Asp Ile Gln Lys Ala Gln Val Ser Gly Gln Gly Asp Ser Leu
705 710 715 720

His Glu His Ile Ala Asn Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly
725 730 735

Ile Leu Gln Thr Val Lys Val Val Asp Glu Leu Val Lys Val Met Gly
740 745 750

Arg His Lys Pro Glu Asn Ile Val Ile Glu Met Ala Arg Glu Asn Gln
755 760 765

Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu Arg Met Lys Arg Ile
770 775 780

Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile Leu Lys Glu His Pro
785 790 795 800

Val Glu Asn Thr Gln Leu Gln Asn Glu Lys Leu Tyr Leu Tyr Tyr Leu
805 810 815

Gln Asn Gly Arg Asp Met Tyr Val Asp Gln Glu Leu Asp Ile Asn Arg
820 825 830

Leu Ser Asp Tyr Asp Val Asp His Ile Val Pro Gln Ser Phe Leu Lys
835 840 845

Asp Asp Ser Ile Asp Asn Lys Val Leu Thr Arg Ser Asp Lys Asn Arg
850 855 860

Gly Lys Ser Asp Asn Val Pro Ser Glu Glu Val Val Lys Lys Met Lys

865	870	875	880
Asn Tyr Trp Arg Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys			
885	890	895	
Phe Asp Asn Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp			
900	905	910	
Lys Ala Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr			
915	920	925	
Lys His Val Ala Gln Ile Leu Asp Ser Arg Met Asn Thr Lys Tyr Asp			
930	935	940	
Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys Ser			
945	950	955	960
Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys Val Arg			
965	970	975	
Glu Ile Asn Asn Tyr His His Ala His Asp Ala Tyr Leu Asn Ala Val			
980	985	990	
Val Gly Thr Ala Leu Ile Lys Lys Tyr Pro Lys Leu Glu Ser Glu Phe			
995	1000	1005	
Val Tyr Gly Asp Tyr Lys Val Tyr Asp Val Arg Lys Met Ile Ala			
1010	1015	1020	
Lys Ser Glu Gln Glu Ile Gly Lys Ala Thr Ala Lys Tyr Phe Phe			
1025	1030	1035	
Tyr Ser Asn Ile Met Asn Phe Phe Lys Thr Glu Ile Thr Leu Ala			
1040	1045	1050	
Asn Gly Glu Ile Arg Lys Arg Pro Leu Ile Glu Thr Asn Gly Glu			
1055	1060	1065	
Thr Gly Glu Ile Val Trp Asp Lys Gly Arg Asp Phe Ala Thr Val			
1070	1075	1080	
Arg Lys Val Leu Ser Met Pro Gln Val Asn Ile Val Lys Lys Thr			
1085	1090	1095	

Glu Val Gln Thr Gly Gly Phe Ser Lys Glu Ser Ile Leu Pro Lys
1100 1105 1110

Arg Asn Ser Asp Lys Leu Ile Ala Arg Lys Lys Asp Trp Asp Pro
1115 1120 1125

Lys Lys Tyr Gly Gly Phe Asp Ser Pro Thr Val Ala Tyr Ser Val
1130 1135 1140

Leu Val Val Ala Lys Val Glu Lys Gly Lys Ser Lys Lys Leu Lys
1145 1150 1155

Ser Val Lys Glu Leu Leu Gly Ile Thr Ile Met Glu Arg Ser Ser
1160 1165 1170

Phe Glu Lys Asn Pro Ile Asp Phe Leu Glu Ala Lys Gly Tyr Lys
1175 1180 1185

Glu Val Lys Lys Asp Leu Ile Ile Lys Leu Pro Lys Tyr Ser Leu
1190 1195 1200

Phe Glu Leu Glu Asn Gly Arg Lys Arg Met Leu Ala Ser Ala Gly
1205 1210 1215

Glu Leu Gln Lys Gly Asn Glu Leu Ala Leu Pro Ser Lys Tyr Val
1220 1225 1230

Asn Phe Leu Tyr Leu Ala Ser His Tyr Glu Lys Leu Lys Gly Ser
1235 1240 1245

Pro Glu Asp Asn Glu Gln Lys Gln Leu Phe Val Glu Gln His Lys
1250 1255 1260

His Tyr Leu Asp Glu Ile Ile Glu Gln Ile Ser Glu Phe Ser Lys
1265 1270 1275

Arg Val Ile Leu Ala Asp Ala Asn Leu Asp Lys Val Leu Ser Ala
1280 1285 1290

Tyr Asn Lys His Arg Asp Lys Pro Ile Arg Glu Gln Ala Glu Asn
1295 1300 1305

Ile Ile His Leu Phe Thr Leu Thr Asn Leu Gly Ala Pro Ala Ala
1310 1315 1320

Phe Lys Tyr Phe Asp Thr Thr Ile Asp Arg Lys Arg Tyr Thr Ser
1325 1330 1335

Thr Lys Glu Val Leu Asp Ala Thr Leu Ile His Gln Ser Ile Thr
1340 1345 1350

Gly Leu Tyr Glu Thr Arg Ile Asp Leu Ser Gln Leu Gly Gly Asp
1355 1360 1365

Gly Ser Gly Ser Pro Lys Lys Lys Arg Lys Val Asp Gly Ser Pro
1370 1375 1380

Lys Lys Lys Arg Lys Val Asp Ser Gly
1385 1390

<210> 226
<211> 4179
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: ORF del ARNm de la nickasa Cas9 que codifica la SEQ ID NO: 25 que usa
codones de mínima uridina como se enumeran en la Tabla 3, sin codones
de inicio y parada

<400> 226
auggacaaga aguacagcau cggacuggca aucggaacaa acagcgucgg augggcaguc 60
aucacagacg aaaucaaggu cccgagcaag aaguucaagg uccugggaaa cacagacaga 120
cacagcauca agaagaaccu gaucggagca cugcuguucg acagcggaga aacagcagaa 180
gcaacaagac ugaagagaac agcaagaaga agauacacaa gaagaaagaa cagaaucugc 240
uaccugcagg aaaucuucag caacgaaaug gcaaaggucg acgacagcuu cuuccacaga 300
cuggaagaaa gcuuccuggu cgaagaagac aagaagcacg aaagacaccc gaucuucgga 360
aacaucgucg acgaagucgc auaccacgaa aaguaccgga caaucuacca ccugagaaag 420
aagcuggucg acagcacaga caaggcagac cugagacuga ucuaccuggc acuggcacac 480
augaucaagu ucagaggaca cuuccugauc gaaggagacc ugaaccgga caacagcgac 540
gucgacaagc uguucaucca gcugguccag acauacaacc agcuguucga agaaaaccg 600
aucaacgcaa gcggagucga cgcaaaggca auccugagcg caagacugag caagagcaga 660
agacuggaaa accugaucgc acagcugccg ggagaaaaga agaacggacu guucggaaac 720
cugaucgcac ugagccuggg acugacaccg aacuuaaga gcaacuucga ccuggcagaa 780
gacgcaaagc ugcagcugag caaggacaca uacgacgacg accuggacaa ccugcuggca 840

cagaucggag accaguacgc agaccuguuc cuggcagcaa agaaccugag cgacgcaauc	900
cugcugagcg acauccugag agucaacaca gaaaucacaa aggcaccgcu gagcgcaagc	960
augaucaaga gauacgacga acaccaccag gaccugacac ugcugaaggc acuggucaga	1020
cagcagcugc cggaaaagua caaggaaauc uucuucgacc agagcaagaa cggauacgca	1080
ggauacaucg acggaggagc aagccaggaa gaauucuaca aguucauca gccgauccug	1140
gaaaagaugg acggaacaga agaacugcug gucaagcuga acagagaaga ccugcugaga	1200
aagcagagaa cauucgacaa cggaagcauc ccgcaccaga uccaccuggg agaacugcac	1260
gcaauccuga gaagacagga agacuucuac ccguuccuga aggacaacag agaaaagauc	1320
gaaaagaucc ugacauucag aaucccgua uacgucggac cgcuggcaag aggaaacagc	1380
agauucgcau ggaugacaag aaagagcgaa gaaacaauca caccugggaa cuucgaagaa	1440
gucgucgaca agggagcaag cgcacagagc uucaucgaaa gaaugacaaa cuucgacaag	1500
aaccugccga acgaaaaggu ccugccgaag cacagccugc uguacgaaua cuucacaguc	1560
uacaacgaac ugacaaaggu caaguacguc acagaaggaa ugagaaagcc ggcauuccug	1620
agcggagaac agaagaaggc aaucgucgac cugcuguuca agacaaacag aaaggucaca	1680
gucaagcagc ugaaggaaga cuacuucaag aagaucgaau gcuucgacag cgucgaaauc	1740
agcggagucg aagacagauu caacgcaagc cugggaacau accacgaccu gcugaagauc	1800
aucaaggaca aggacuuccu ggacaacgaa gaaaacgaag acauccugga agacaucguc	1860
cugacacuga cacuguucga agacagagaa augaucgaag aaagacugaa gacauacgca	1920
caccuguucg acgacaaggu caugaagcag cugaagagaa gaagauacac aggaugggga	1980
agacugagca gaaagcugau caacggaauc agagacaagc agagcggaaa gacaauccug	2040
gacuuccuga agagcgacgg auucgcaaac agaaacuuca ugcagcugau ccacgacgac	2100
agccugacau ucaaggaaga cauccagaag gcacagguca gcggacaggg agacagccug	2160
cacgaacaca ucgcaaaccu ggcaaggagc ccggcaauca agaagggaau ccugcagaca	2220
gucaaggucg ucgacgaacu ggucaagguc augggaagac acaagccgga aaacaucguc	2280
aucgaaaugg caagagaaaa ccagacaaca cagaaggagc agaagaacag cagagaaaga	2340
augaagagaa ucgaagaagg aaucaggaa cugggaagcc agauccugaa ggaacacccg	2400
gucgaaaaca cacagcugca gaacgaaaag cuguaccugu acuaccugca gaacggaaga	2460
gacauguacg ucgaccagga acuggacauc aacagacuga gcgacuacga cgucgaccac	2520
aucguccgc agagcuuccu gaaggacgac agcaucgaca acaagguccu gacaagaagc	2580

gacaagaaca gaggaaagag cgacaacguc ccgagcgaag aagucgucaa gaagaugaag	2640
aacuacugga gacagcugcu gaacgcaaag cugaucacac agagaaaguu cgacaaccug	2700
acaaaggcag agagaggagg acugagcgaa cuggacaagg caggauucau caagagacag	2760
cuggucgaaa caagacagau cacaagcac gucgcacaga uccuggacag cagaaugaac	2820
acaaaguacg acgaaaacga caagcugauc agagaaguca aggucaucac acugaagagc	2880
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uaccaccacg cacacgacgc auaccugaac gcagucgucg gaacagcacu gaucaagaag	3000
uacccgaagc uggaagcga auucgucuac ggagacuaca agguacuaga cgucagaaag	3060
augaucgcaa agagcgaaca ggaaaucgga aaggcaacag caaguacuu cuucuacagc	3120
aacaucauga acuucuuaa gacagaaauc acacuggcaa acggagaaau cagaaagaga	3180
ccgcugaucg aaacaaacgg agaaacagga gaaucgucu gggacaaggg aagagacuuc	3240
gcaacaguca gaaagguccu gagcaugccg cagguaaca ucgucaagaa gacagaaguc	3300
cagacaggag gauucagcaa ggaaagcauc cugccgaaga gaaacagcga caagcugauc	3360
gcaagaaaga aggacuggga cccgaagaag uacggaggau ucgacagccc gacagucgca	3420
uacagcgucc ugguucgucg aaaggucgaa aagggaaga gcaagaagcu gaagagcguc	3480
aaggaacugc uggaauacac aaucaggga agaagcagcu ucgaaaagaa cccgaucgac	3540
uuccuggaag caaagggaau caaggaaguc aagaaggacc ugaucauaa gcugccgaag	3600
uacagccugu ucgaacugga aaacggaaga aagagaauuc uggaagcgc aggagaacug	3660
cagaaggga acgaacuggc acugccgagc aaguacguca acuuccugua ccuggcaagc	3720
cacuacgaaa agcugaaggg aagcccgga gacaacgaac agaagcagcu guucgucgaa	3780
cagcacaagc acuaccugga cgaaauauc gaacagauca gcgaauucag caagagaguc	3840
auccuggcag acgcaaaccu ggacaagguc cugagcgcau acaacaagca cagagacaag	3900
ccgaucagag aacaggcaga aaacauauc caccuguuca cacugacaaa ccugggagca	3960
ccggcagcau ucaaguacuu cgacacaaca aucgacagaa agagauacac aagcaciaag	4020
gaaguccugg acgcaacacu gauccaccag agcaucacag gacuguacga aacaagauc	4080
gaccugagcc agcugggagg agacggaagc ggaagcccga agaagaagag aaaggucgac	4140
ggaagcccga agaagaagag aaaggucgac agcggauag	4179

<210> 227
 <211> 4173
 <212> ARN
 <213> Secuencia artificial

<220>

<223> Sintético: secuencia de codificación de la nickasa Cas9 que codifica la SEQ ID NO: 25 que usa codones de mínima uridina (sin codones de inicio y parada; adecuada para su inclusión en la secuencia de codificación de proteínas de fusión)

<400> 227

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acagacgaau acaagguccc gagcaagaag uucaaggucc ugaggaaacac agacagacac	120
agcaucaaga agaaccugau cggagcacug cuguucgaca gcggagaaac agcagaagca	180
acaagacuga agagaacagc aagaagaaga uacacaagaa gaaagaacag aaucugcuac	240
cugcaggaaa ucuucagcaa cgaauggca aaggucgacg acagcuucuu ccacagacug	300
gaagaaagcu uccuggucga agaagacaag aagcacgaaa gacacccgau cuucggaaac	360
aucgucgacg aagucgcaua ccacgaaaag uacccgacaa ucuaccaccu gagaaagaag	420
cuggucgaca gcacagacaa ggcagaccug agacugaucu accuggcacu ggcacacaug	480
aucaaguuca gaggacacuu ccugaucgaa ggagaccuga acccggacaa cagcgacguc	540
gacaagcugu ucauccagcu gguccagaca uacaaccagc uguucgaaga aaacccgauc	600
aacgcaagcg gagucgacgc aaaggcaauc cugagcgcaa gacugagcaa gagcagaaga	660
cuggaaaacc ugaucgcaca gcugccggga gaaaagaaga acggacuguu cggaaccug	720
aucgcacuga gccugggacu gacaccgaac uucaagagca acuucgaccu ggcagaagac	780
gcaaagcugc agcugagcaa ggacacauac gacgacgacc uggacaaccu gcuggcacag	840
aucggagacc aguacgcaga ccuguuccug gcagcaaaga accugagcga cgcaauccug	900
cugagcgaca uccugagagu caacacagaa aucacaaagg caccgcugag cgcaagcaug	960
aucaagagau acgacgaaca ccaccaggac cugacacugc ugaaggcacu ggucagacag	1020
cagcugccgg aaaaguacaa ggaaaucuuc uucgaccaga gcaagaacgg auacgcagga	1080
uacaucgacg gaggagcaag ccaggaagaa uucaacaagu ucaucaagcc gaucuggaa	1140
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cagagaacau ugcacaacgg aagcaucccg caccagaucc accugggaga acugcacgca	1260
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aagauccuga cauucagaau cccguacuac gucggaccgc uggcaagagg aaacagcaga	1380
uucgcaugga ugacaagaaa gagcgaagaa acauacacac cguggaacuu cgaagaaguc	1440
gucgacaagg gagcaagcgc acagagcuuc aucgaaagaa ugacaaacuu cgacaagaac	1500
cugccgaacg aaaagguccu gccgaagcac agccugcugu acgaauacuu cacagucuac	1560

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 ggagaacaga agaaggcaau cgucgaccug cuguucaaga caaacagaaa ggucacaguc 1680
 aagcagcuga aggaagacua cuucaagaag aucgaaugcu ucgacagcgu cgaaucagc 1740
 ggagucgaag acagauuca cgcaagccug ggaacauacc acgaccugcu gaagaucauc 1800
 aaggacaagg acuuccugga caacgaagaa aacgaagaca uccuggaaga caucguccug 1860
 acacugacac uguucgaaga cagagaaaug aucgaagaaa gacugaagac auacgcacac 1920
 cuguucgacg acaaggucau gaagcagcug aagagaagaa gauacacagg auggggaaga 1980
 cugagcagaa agcugaucaa cggaaucaga gacaagcaga gcggaaagac aauccuggac 2040
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 aucgcaaaga gcgaacagga aaucggaaag gcaacagcaa aguacuucuu cuacagcaac 3120
 aucaugaacu ucuucaagac agaaucaca cuggcaaagc gagaaucag aaagagaccg 3180
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agcccgaaga agaagagaaa ggucgacagc gga 4173

<210> 228
<211> 1392
<212> PRT
<213> Secuencia artificial

<220>
<223> Sintético: Secuencia de aminoácidos de dCas9 con dos señales de localización nuclear
como los aminoácidos C-terminales

<400> 228

Met Asp Lys Lys Tyr Ser Ile Gly Leu Ala Ile Gly Thr Asn Ser Val
1 5 10 15

Gly Trp Ala Val Ile Thr Asp Glu Tyr Lys Val Pro Ser Lys Lys Phe
20 25 30

Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys Lys Asn Leu Ile
35 40 45

Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu
50 55 60

Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys
65 70 75 80

Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met Ala Lys Val Asp Asp Ser
85 90 95

Phe Phe His Arg Leu Glu Glu Ser Phe Leu Val Glu Glu Asp Lys Lys
100 105 110

His Glu Arg His Pro Ile Phe Gly Asn Ile Val Asp Glu Val Ala Tyr
115 120 125

His Glu Lys Tyr Pro Thr Ile Tyr His Leu Arg Lys Lys Leu Val Asp
130 135 140

Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile Tyr Leu Ala Leu Ala His
145 150 155 160

Met Ile Lys Phe Arg Gly His Phe Leu Ile Glu Gly Asp Leu Asn Pro
165 170 175

Asp Asn Ser Asp Val Asp Lys Leu Phe Ile Gln Leu Val Gln Thr Tyr
180 185 190

Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn Ala Ser Gly Val Asp Ala
195 200 205

Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys Ser Arg Arg Leu Glu Asn
210 215 220

Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys Asn Gly Leu Phe Gly Asn
225 230 235 240

Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro Asn Phe Lys Ser Asn Phe
245 250 255

Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu Ser Lys Asp Thr Tyr Asp
260 265 270

Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile Gly Asp Gln Tyr Ala Asp
275 280 285

Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp Ala Ile Leu Leu Ser Asp
290 295 300

Ile Leu Arg Val Asn Thr Glu Ile Thr Lys Ala Pro Leu Ser Ala Ser

305310315320

Met Ile Lys Arg Tyr Asp Glu His His Gln Asp Leu Thr Leu Leu Lys

325330335

Ala Leu Val Arg Gln Gln Leu Pro Glu Lys Tyr Lys Glu Ile Phe Phe

340345350

Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr Ile Asp Gly Gly Ala Ser

355360365

Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro Ile Leu Glu Lys Met Asp

370375380

Gly Thr Glu Glu Leu Leu Val Lys Leu Asn Arg Glu Asp Leu Leu Arg

385390395400

Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile Pro His Gln Ile His Leu

405410415

Gly Glu Leu His Ala Ile Leu Arg Arg Gln Glu Asp Phe Tyr Pro Phe

420425430

Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile

435440445

Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp

450455460

Met Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu

465470475480

Val Val Asp Lys Gly Ala Ser Ala Gln Ser Phe Ile Glu Arg Met Thr

485490495

Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys Val Leu Pro Lys His Ser

500505510

Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu Leu Thr Lys Val Lys

515520525

Tyr Val Thr Glu Gly Met Arg Lys Pro Ala Phe Leu Ser Gly Glu Gln

530535540

Lys Lys Ala Ile Val Asp Leu Leu Phe Lys Thr Asn Arg Lys Val Thr
545 550 555 560

Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp
 565 570 575

Ser Val Glu Ile Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu Gly
 580 585 590

Thr Tyr His Asp Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp
 595 600 605

Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile Val Leu Thr Leu Thr
 610 615 620

Leu Phe Glu Asp Arg Glu Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala
625 630 635 640

His Leu Phe Asp Asp Lys Val Met Lys Gln Leu Lys Arg Arg Arg Tyr
 645 650 655

Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp
 660 665 670

Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe
 675 680 685

Ala Asn Arg Asn Phe Met Gln Leu Ile His Asp Asp Ser Leu Thr Phe
 690 695 700

Lys Glu Asp Ile Gln Lys Ala Gln Val Ser Gly Gln Gly Asp Ser Leu
705 710 715 720

His Glu His Ile Ala Asn Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly
 725 730 735

Ile Leu Gln Thr Val Lys Val Val Asp Glu Leu Val Lys Val Met Gly
 740 745 750

Arg His Lys Pro Glu Asn Ile Val Ile Glu Met Ala Arg Glu Asn Gln
 755 760 765

Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu Arg Met Lys Arg Ile
 770 775 780

Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile Leu Lys Glu His Pro
785 790 795 800

Val Glu Asn Thr Gln Leu Gln Asn Glu Lys Leu Tyr Leu Tyr Tyr Leu
 805 810 815

Gln Asn Gly Arg Asp Met Tyr Val Asp Gln Glu Leu Asp Ile Asn Arg
 820 825 830

Leu Ser Asp Tyr Asp Val Asp Ala Ile Val Pro Gln Ser Phe Leu Lys
 835 840 845

Asp Asp Ser Ile Asp Asn Lys Val Leu Thr Arg Ser Asp Lys Asn Arg
 850 855 860

Gly Lys Ser Asp Asn Val Pro Ser Glu Glu Val Val Lys Lys Met Lys
865 870 875 880

Asn Tyr Trp Arg Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys
 885 890 895

Phe Asp Asn Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp
 900 905 910

Lys Ala Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr
 915 920 925

Lys His Val Ala Gln Ile Leu Asp Ser Arg Met Asn Thr Lys Tyr Asp
 930 935 940

Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys Ser
945 950 955 960

Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys Val Arg
 965 970 975

Glu Ile Asn Asn Tyr His His Ala His Asp Ala Tyr Leu Asn Ala Val
 980 985 990

Val Gly Thr Ala Leu Ile Lys Lys Tyr Pro Lys Leu Glu Ser Glu Phe
 995 1000 1005

Val Tyr Gly Asp Tyr Lys Val Tyr Asp Val Arg Lys Met Ile Ala
 1010 1015 1020

Lys Ser Glu Gln Glu Ile Gly Lys Ala Thr Ala Lys Tyr Phe Phe
1025 1030 1035

Tyr Ser Asn Ile Met Asn Phe Phe Lys Thr Glu Ile Thr Leu Ala
1040 1045 1050

Asn Gly Glu Ile Arg Lys Arg Pro Leu Ile Glu Thr Asn Gly Glu
1055 1060 1065

Thr Gly Glu Ile Val Trp Asp Lys Gly Arg Asp Phe Ala Thr Val
1070 1075 1080

Arg Lys Val Leu Ser Met Pro Gln Val Asn Ile Val Lys Lys Thr
1085 1090 1095

Glu Val Gln Thr Gly Gly Phe Ser Lys Glu Ser Ile Leu Pro Lys
1100 1105 1110

Arg Asn Ser Asp Lys Leu Ile Ala Arg Lys Lys Asp Trp Asp Pro
1115 1120 1125

Lys Lys Tyr Gly Gly Phe Asp Ser Pro Thr Val Ala Tyr Ser Val
1130 1135 1140

Leu Val Val Ala Lys Val Glu Lys Gly Lys Ser Lys Lys Leu Lys
1145 1150 1155

Ser Val Lys Glu Leu Leu Gly Ile Thr Ile Met Glu Arg Ser Ser
1160 1165 1170

Phe Glu Lys Asn Pro Ile Asp Phe Leu Glu Ala Lys Gly Tyr Lys
1175 1180 1185

Glu Val Lys Lys Asp Leu Ile Ile Lys Leu Pro Lys Tyr Ser Leu
1190 1195 1200

Phe Glu Leu Glu Asn Gly Arg Lys Arg Met Leu Ala Ser Ala Gly
1205 1210 1215

Glu Leu Gln Lys Gly Asn Glu Leu Ala Leu Pro Ser Lys Tyr Val
1220 1225 1230

Asn Phe Leu Tyr Leu Ala Ser His Tyr Glu Lys Leu Lys Gly Ser

1235	1240	1245
Pro Glu Asp Asn Glu Gln Lys	Gln Leu Phe Val Glu Gln His Lys	
1250	1255	1260
His Tyr Leu Asp Glu Ile Ile	Glu Gln Ile Ser Glu Phe Ser Lys	
1265	1270	1275
Arg Val Ile Leu Ala Asp Ala	Asn Leu Asp Lys Val Leu Ser Ala	
1280	1285	1290
Tyr Asn Lys His Arg Asp Lys	Pro Ile Arg Glu Gln Ala Glu Asn	
1295	1300	1305
Ile Ile His Leu Phe Thr Leu	Thr Asn Leu Gly Ala Pro Ala Ala	
1310	1315	1320
Phe Lys Tyr Phe Asp Thr Thr	Ile Asp Arg Lys Arg Tyr Thr Ser	
1325	1330	1335
Thr Lys Glu Val Leu Asp Ala	Thr Leu Ile His Gln Ser Ile Thr	
1340	1345	1350
Gly Leu Tyr Glu Thr Arg Ile	Asp Leu Ser Gln Leu Gly Gly Asp	
1355	1360	1365
Gly Ser Gly Ser Pro Lys Lys	Lys Arg Lys Val Asp Gly Ser Pro	
1370	1375	1380
Lys Lys Lys Arg Lys Val Asp	Ser Gly	
1385	1390	

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uaccugcagg aaaucuucag caacgaaaug gcaaaggucg acgacagcuu cuuccacaga	300
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aacaucgucg acgaagucgc auaccacgaa aaguacccga caaucuacca ccugagaaag	420
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gucgacaagc uguucaucca gcugguccag acauacaacc agcuguucga agaaaacccg	600
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cagaucggag accaguacgc agaccuguuc cuggcagcaa agaaccugag cgacgcauc	900
cugcugagcg acauccugag agucaacaca gaaucacaa aggcaccgcu gagcgcaagc	960
augaucaaga gauacgacga acaccaccag gaccugacac ugcugaaggc acuggucaga	1020
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ggauacaucg acggaggagc aagccaggaa gaauucuaca aguucauca gccgauccug	1140
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aagcagagaa cauucgacaa cggaagcauc ccgcaccaga uccaccuggg agaacugcac	1260
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gucgucgaca agggagcaag cgcacagagc uucaucgaaa gaaugacaaa cuucgacaag	1500
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uacaacgaac ugacaaaggu caaguacguc acagaaggaa ugagaaagcc ggcauuccug	1620
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aucaaggaca aggacuuccu ggacaacgaa gaaaacgaag acauccugga agaucguc	1860
cugacacuga cacuguucga agacagagaa augaucgaag aaagacugaa gacauacgca	1920
caccuguucg acgacaaggu caugaagcag cugaagagaa gaagauacac aggaugggga	1980

agacugagca gaaagcugau caacggaauc agagacaagc agagcggaaa gacaauccug	2040
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ccgcugaucg aaacaaacgg agaaacagga gaaucgucu gggacaaggg aagagacuuc	3240
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<210> 230

<211> 4173

<212> ARN

<213> Secuencia artificial

<220>

<223> Sintético: secuencia de codifiación de dCas9 que codifica la SEQ ID NO: 228 que usa codones de mínima uridina (sin codones de inicio y parada; adecuada para su inclusión en la secuencia de codificación de proteínas de fusión)

<400> 230

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agcaucaaga agaaccugau cggagcacug cuguucgaca gcggagaaac agcagaagca	180
acaagacuga agagaacagc aagaagaaga uacacaagaa gaaagaacag aaucugcuac	240
cugcaggaaa ucuucagcaa cgaaauaggca aaggucgacg acagcuucuu ccacagacug	300
gaagaaagcu uccuggucga agaagacaag aagcacgaaa gacacccgau cuucggaaac	360
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cuggucgaca gcacagacaa ggcagaccug agacugaucu accuggcacu ggcacacaug	480
aucaaguuca gaggacacuu ccugaucgaa ggagaccuga acccggacaa cagcgacguc	540
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aacgcaagcg gagucgacgc aaaggcauc cugagcgcaa gacugagcaa gagcagaaga	660
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uacaucgacg gaggagcaag ccaggaagaa uucuacaagu ucaucaagcc gauccuggaa	1140
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agcccgaaga agaagagaaa ggucgacagc gga 4173

- <210> 231
- <211> 17
- <212> ADN
- <213> Secuencia artificial

- <220>
- <223> Sintético: Promotor T7

<400> 231
taatacgact cactata17

<210> 232
<211> 50
<212> ADN
<213> Homo sapiens

<220>
<221> misc_característica
<222> (1)..(50)
<223> Beta-globina humana 5 UTR

<400> 232
acatttgctt ctgacacaac tgtgttcact agcaacctca aacagacacc50

<210> 233
<211> 132
<212> ADN
<213> Homo sapiens

<220>
<221> misc_característica
<222> (1)..(132)
<223> Beta-globina humana 3 UTR

<400> 233
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taaactgggg gatattatga agggccttga gcatctggat tctgcctaataaaaaacatt120

tattttcatt gc132

<210> 234
<211> 66
<212> ADN
<213> Homo sapiens

<220>
<221> misc_característica
<222> (1)..(66)
<223> Alfa-globina humana 5 UTR

<400> 234
cataaacctt ggcgcgctcg cggcccgga ctcttctggt cccacagac tcagagagaa60

cccacc66

<210> 235
<211> 110
<212> ADN
<213> Homo sapiens

<220>
<221> misc_característica
<222> (1)..(110)
<223> Alfa-globina humana 3 UTR

<400> 235
gctggagcct cggtaggcat gcttcttgcc ccttgggcct cccccagcc cctcctcccc 60

ttcctgcacc cgtacccccg tggcttttga ataaagtctg agtgggcggc 110

<210> 236
<211> 29
<212> ADN
<213> Xenopus laevis

<220>
<221> misc_característica
<222> (1)..(29)
<223> beta-globina 5 UTR de Xenopus laevis

<400> 236
aagctcagaa taaacgctca actttggcc 29

<210> 237
<211> 130
<212> ADN
<213> Xenopus laevis

<220>
<221> misc_característica
<222> (1)..(130)
<223> beta-globina 3' UTR de Xenopus laevis

<400> 237
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caaaatgttg tcccccaaaa ttagccatt cgtatctgct cctaataaaa agaaagtffc 120

ttcacattct 130

<210> 238
<211> 27
<212> ADN
<213> Bos taurus

<220>
<221> misc_característica
<222> (1)..(27)
<223> Hormona de crecimiento bovina 5 UTR

<400> 238

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27

<210> 239
<211> 102
<212> ADN
<213> Bos taurus

<220>
<221> misc_característica
<222> (1)..(102)
<223> Hormona de crecimiento bovina 3 UTR

<400> 239
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tcccactgtc ctttctaataaaaatgagga aattgcatcg ca 102

<210> 240
<211> 93
<212> ADN
<213> Mus musculus

<220>
<221> misc_característica
<222> (1)..(93)
<223> Hemoglobina alfa de Mus musculus, cadena adulta 1 (Hba-a1), 3UTR

<400> 240
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ctcttggtct ttgaataaag cctgagtagg aag 93

<210> 241
<211> 61
<212> ADN
<213> Secuencia artificial

<220>
<223> Sintético: HSD17B4 5 UTR

<400> 241
tccgcagtc ggcgtccagc ggctctgctt gttcgtgtgt gtgtcgttgc aggccttatt 60

c 61

<210> 242
<211> 100
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: ARN de guía única G282 dirigido al gen TTR de ratón

<220>
<221> base_modificada
<222> (1)..(3)
<223> Enlace PS, nucleótido 2'-O-Me

<220>
<221> base_modificada
<222> (29)..(40)
<223> nucleótido 2'-O-Me

<220>
<221> base_modificada
<222> (69)..(96)
<223> nucleótido 2'-O-Me

<220>
<221> base_modificada
<222> (97)..(100)
<223> Enlace PS, nucleótido 2'-O-Me

<400> 242
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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 243

<400> 243
000

<210> 244
<211> 4405
<212> ADN
<213> Secuencia artificial

<220>
<223> Sintético: transcrito de Cas9 con 5 UTR de HSD, ORF correspondiente a la
SEQ ID NO: 204, y 3 UTR de ALB

<400> 244
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atgggcagtc atcacagacg aatacaaggt cccgagcaag aagttcaagg tcctgggaaa 180

cacagacaga cacagcatca agaagaacct gatcggagca ctgctgttcg acagcggaga 240

aacagcagaa gcaacaagac tgaagagaac agcaagaaga agatacaca gaagaaagaa 300

cagaatctgc tacctgcagg aaatcttcag caacgaaatg gcaaaggctg acgacagctt 360

cttcacaga ctggaagaaa gcttcttggt cgaagaagac aagaagcacg aaagacaccc 420

gatcttcgga aacatcgtcg acgaagtcgc ataccacgaa aagtaccga caatctacca 480

cctgagaaag aagctggtcg acagcacaga caaggcagac ctgagactga tctacctggc 540

actggcacac atgatcaagt tcagaggaca cttcctgac gaaggagacc tgaacccgga 600
 caacagcgac gtcgacaagc tgttcatcca gctggtccag acatacaacc agctgttcga 660
 agaaaacccg atcaacgcaa gcggagtcga cgcaaaggca atcctgagcg caagactgag 720
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<210> 245
<211> 4188
<212> ADN
<213> Secuencia artificial

<220>
<223> Sintético: ORF de Cas9 alternativo con 19.36 % de contenido de U

<400> 245
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cacagcatca agaagaatct catcggagcc ctgctgtttg actccggcga aaccgcagaa 180
gcgacccggc tcaaacgtac cgcgaggcga cgctacaccc ggcggaagaa tcgcatctgc 240
tatctgcaag aaatcttttc gaacgaaatg gcaaagggtg acgacagctt cttccaccgc 300
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aagttggtg actcaactga caaggccgac ctgagattga tctacttggc cctcgcccat 480
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<210> 246

<211> 4459

<212> ADN

<213> Secuencia artificial

<220>

<223> Sintético: transcrito de Cas9 con 5 UTR de HSD, ORF correspondiente a la
SEQ ID NO: 245, secuencia de Kozak, y 3 UTR de ALB

<400> 246

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aatggaaag aacctcgag 4459

<210> 247
<211> 4453
<212> ADN
<213> Secuencia artificial

<220>
<223> Sintético: transcrito de Cas9 con 5 UTR de HSD, ORF correspondiente de la
SEQ ID NO: 245, y 3 UTR de ALB

<400> 247
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<210> 248

<400> 248
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<210> 249
<211> 4409
<212> ADN
<213> Secuencia artificial

<220>
<223> Sintético: transcrito de Cas9 que comprende la secuencia de Kozak con ORF de Cas9
que usa codones con expresión generalmente alta en humanos

<400> 249
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<210> 250
<211> 4140
<212> ADN
<213> Secuencia artificial

<220>
<223> Sintético: ORF de Cas9 con uniones de empalme eliminadas; 12.75 % de contenido de U

<400> 250

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cacagcatca agaagaacct gatcggagca ctgctgttcg acagcggaga aacagcagaa	180
gcaacaagac tgaagagaac agcaagaaga agatacaca gaagaaagaa cagaatctgc	240
tacctgcagg aaatcttcag caacgaaatg gcaaaggctg acgacagctt cttccaccgg	300
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<210> 251
<211> 4411
<212> ADN
<213> Secuencia artificial

<220>
<223> Sintético: transcrito de Cas9 con 5 UTR de HSD, ORF correspondiente a la
SEQ ID NO: 250, secuencia de Kozak, y 3 UTR de ALB

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<210> 252
<211> 4140
<212> ADN
<213> Secuencia artificial

<220>
<223> Sintético: ORF de Cas9 con codones de mínima uridina de uso frecuente en humanos
en general; 12.75 % de contenido de U

<400> 252
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cacagcatca agaagaacct gatcggcgcc ctgctgttcg acagcggcga gaccgccgag 180
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<210> 253

<211> 4411

<212> ADN

<213> Secuencia artificial

<220>

<223> Sintético: transcrito de Cas9 con 5 UTR de HSD, ORF correspondiente a la
SEQ ID NO: 252, secuencia de Kozak, y 3 UTR de ALB

<400> 253

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<210> 254

<211> 4140

<212> ADN

<213> Secuencia artificial

<220>

<223> Sintético: ORF de Cas9 con codones de mínima uridina usados con poca frecuencia en humanos en general; 12.75 % de contenido de U

<400> 254

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ccggcggcgt tcaaatactt cgacacgacg atagaccgaa aacgatacac gagcacgaaa 4020
gaagtactag acgcgacgct aatacaccaa agcataacgg ggctatacga aacgcgaata 4080
gacctaagcc aactaggggg ggacgggggg gggagcccga aaaaaaacg aaaagtatga 4140

<211> 4411
<212> ADN
<213> Secuencia artificial

<220>
<223> Sintético: transcrito de Cas9 con 5 UTR de HSD, ORF correspondiente a la
SEQ ID NO: 254, secuencia de Kozak, y 3 UTR de ALB

<400> 255
gggtcccga gtcggcgctc agcggctctg cttgttcgtg tgtgtgtcgt tgcaggcctt 60

attcggatcc gccaccatgg acaaaaaata cagcataggg ctagacatag ggacgaacag 120

cgtagggtgg gcggtataa cggacgaata caaagtaccg agcaaaaaat tcaaagtact 180

agggaacacg gaccgacaca gcataaaaaa aaacctaata ggggcgctac tattcgacag 240

cggggaaacg gcggaagcga cgcgactaaa acgaacggcg cgacgacgat acacgcgacg 300

aaaaaacga atatgctacc tacaagaaat attcagcaac gaaatggcga aagtagacga 360

cagcttctc caccgactag aagaaagctt ctagtagaa gaagacaaaa aacacgaacg 420

acacccgata ttcgggaaca tagtagacga agtagcgtac cacgaaaaat acccgacgat 480

ataccaccta cgaaaaaac tagtagacag cacggacaaa gcggacctac gactaatata 540

cctagcgcta gcgcacatga taaaattccg agggcacttc ctaatagaag gggacctaaa 600

cccgacaac agcgacgtag acaactatt catacaacta gtacaaacgt acaaccaact 660

attcgaagaa aacccgataa acgcgagcgg ggtagacgcg aaagcgatac taagcgcgcg 720

actaagcaaa agccgacgac tagaaaacct aatagcgcaa ctaccggggg aaaaaaaaaa 780

cgggctattc gggaacctaa tagcgctaag cctagggcta acgccgaact tcaaaagcaa 840

cttcgaccta gcggaagacg cgaaactaca actaagcaaa gacacgtacg acgacgacct 900

agacaaccta ctacgcaaaa taggggacca atacgcggac ctattcctag cggcgaaaaa 960

cctaagcgac gcgatactac taagcgacat actacgagta aacacggaaa taacgaaagc 1020

gccgctaagc gcgagcatga taaaacgata cgacgaacac caccaagacc taacgtact 1080

aaaagcgcta gtacgacaac aactaccgga aaaatacaaa gaaatattct tcgaccaaag 1140

caaaaacggg tacgcggggt acatagacgg gggggcgagc caagaagaat tctacaaatt 1200

cataaaaccg atactagaaa aaatggacgg gacggaagaa ctactagtaa aactaaaccg 1260

agaagaccta ctacgaaaac aacgaacgtt cgacaacggg agcataccgc accaaataca 1320

cctaggggaa ctacacgcga tactacgacg acaagaagac ttctaccgt tcctaaaaga 1380

caaccgagaa aaaatagaaa aaatactaac gttccgaata ccgtactacg tagggccgct 1440

agcgcgaggg aacagccgat tcgctggat gacgcgaaaa agcgaagaaa cgataacgcc 1500

gtggaacttc gaagaagtag tagacaaagg ggcgagcgcg caaagcttca tagaacgaat 1560
 gacgaacttc gacaaaaacc taccgaacga aaaagtacta ccgaaacaca gcctactata 1620
 cgaatacttc acggtataca acgaactaac gaaagtaaaa tacgtaacgg aagggatgcg 1680
 aaaaccggcg ttcctaagcg gggaacaaaa aaaagcgata gtagacctac tattcaaac 1740
 gaaccgaaaa gtaacggtaa aacaactaaa agaagactac ttcaaaaaaa tagaatgctt 1800
 cgacagcgta gaaataagcg gggtagaaga ccgattcaac gcgagcctag ggacgtacca 1860
 cgacctacta aaaataataa aagacaaaga cttcctagac aacgaagaaa acgaagacat 1920
 actagaagac atagtactaa cgctaacgct attcgaagac cgagaaatga tagaagaacg 1980
 actaaaaacg tacgcgcacc tattcgacga caaagtaatg aaacaactaa aacgacgacg 2040
 atacacgggg tgggggcgac taagccgaaa actaataaac gggatacgag acaaacaaag 2100
 cgggaaaacg atactagact tcctaaaaag cgacgggttc gcgaaccgaa acttcatgca 2160
 actaatacac gacgacagcc taacgttcaa agaagacata caaaaagcgc aagtaagcgg 2220
 gcaaggggac agcctacacg aacacatagc gaacctagcg gggagcccgg cgataaaaaa 2280
 agggatacta caaacggtaa aagtagtaga cgaactagta aaagtaatgg ggcgacacaa 2340
 accggaaaac atagtaatag aaatggcgcg agaaaaccaa acgacgcaa aagggcaaaa 2400
 aaacagccga gaacgaatga aacgaataga agaaggata aaagaactag ggagccaaat 2460
 actaaaagaa cccccgtag aaaacacgca actacaaaac gaaaaactat acctatacta 2520
 cctacaaaac gggcgagaca tgtacgtaga ccaagaacta gacataaacc gactaagcga 2580
 ctacgacgta gaccacatag taccgcaaag cttcctaaaa gacgacagca tagacaacaa 2640
 agtactaacg cgaagcgaca aaaaccgagg gaaaagcgac aacgtaccga gcgaagaagt 2700
 agtaaaaaaa atgaaaaact actggcgaca actactaaac gcgaaactaa taacgcaacg 2760
 aaaattcgac aacctaacga aagcggaacg aggggggcta agcgaactag acaaagcggg 2820
 gttcataaaa cgacaactag tagaaacgcg acaataacg aaacacgtag cgcaaatact 2880
 agacagccga atgaacacga aatacgacga aaacgacaaa ctaatacgag aagtaaaagt 2940
 aataacgcta aaaagcaaac tagtaagcga cttccgaaaa gacttccaat tctacaaagt 3000
 acgagaaata aacaactacc accacgcgca cgacgcgtac ctaaacgcgg tagtagggac 3060
 ggcgctaata aaaaaatacc cgaaactaga aagcgaattc gtatacgggg actacaaagt 3120
 atacgacgta cgaaaaatga tagcgaaaag cgaacaagaa atagggaag cgacggcgaa 3180
 atacttctc tacagcaaca taatgaactt cttcaaacg gaaataacgc tagcgaacgg 3240
 ggaaatacga aaacgaccgc taatagaaac gaacggggaa acgggggaaa tagtatggga 3300

caaagggcga gacttcgcga cggtacgaaa agtactaagc atgccgcaag taaacatagt 3360
aaaaaaaacg gaagtacaaa cggggggggtt cagcaaagaa agcatactac cgaaacgaaa 3420
cagcgacaaa ctaatagcgc gaaaaaaaga ctgggacccg aaaaaatacg ggggggttcga 3480
cagcccgacg gtagcgtaca gcgtactagt agtagcgaaa gtagaaaaag ggaaaagcaa 3540
aaaactaaaa agcgtaaaag aactactagg gataacgata atggaacgaa gcagcttcga 3600
aaaaaacccg atagacttcc tagaagcgaa aggggtacaaa gaagtaaaaa aagacctaatt 3660
aataaaacta ccgaaatata gcctattcga actagaaaac gggcgaaaac gaatgctagc 3720
gagcgcgggg gaactacaaa aagggaacga actagcgcta ccgagcaaat acgtaaactt 3780
cctataccta gcgagccact acgaaaaact aaaagggagc ccggaagaca acgaacaaaa 3840
acaactattc gtagaacaac acaaacacta cctagacgaa ataatagaac aaataagcga 3900
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caaacaccga gacaaaccga tacgagaaca agcggaaaac ataatacacc tattcacgct 4020
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atacacgagc acgaaagaag tactagacgc gacgctaata caccaaagca taacggggct 4140
atacgaaacg cgaatagacc taagccaact aggggggggac ggggggggga gcccgaaaaa 4200
aaaacgaaaa gtatgactag ccatcacatt taaaagcatc tcagcctacc atgagaataa 4260
gagaaagaaa atgaagatca atagcttatt catctctttt tcttttcgt tggtgtaaag 4320
ccaacaccct gtctaaaaaa cataaatttc ttaatcatt ttgcctcttt tctctgtgct 4380
tcaattaata aaaaatggaa agaacctcga g 4411

<210> 256

<211> 4411

<212> ADN

<213> Secuencia artificial

<220>

<223> Sintético: transcrito de Cas9 con AGG como los primeros tres nucleótidos para el uso con CleanCapTM, 5 UTR de HSD, ORF correspondiente a la SEQ ID NO: 204, Secuencia de Kozak, y 3 UTR de ALB

<400> 256

agggtcccga gtcggcgtcc agcggctctg cttgttcgtg tgtgtgtcgt tgcaggcctt 60

attcggatcc gccaccatgg acaagaagta cagcatcgga ctggacatcg gaacaaacag 120

cgtcggatgg gcagtcatca cagacgaata caaggtcccg agcaagaagt tcaaggtcct 180

gggaaacaca gacagacaca gcatcaagaa gaacctgac ggagcactgc tggtcgacag 240

cggagaaaca gcagaagcaa caagactgaa gagaacagca agaagaagat acacaagaag 300
 aaagaacaga atctgtacc tgcaggaaat cttcagcaac gaaatggcaa aggtcgacga 360
 cagcttctc cacagactgg aagaaagctt cctggtcgaa gaagacaaga agcacgaaag 420
 acacccgatc ttcgaaaca tcgtcgacga agtcgcatac cacgaaaagt acccgacaat 480
 ctaccacctg agaaagaagc tggtcgacag cacagacaag gcagacctga gactgatcta 540
 cctggcactg gcacacatga tcaagttcag aggacacttc ctgatcgaag gagacctgaa 600
 cccggacaac agcgacgtcg acaagctgtt catccagctg gtccagacat acaaccagct 660
 gttcgaagaa aacccgatca acgcaagcgg agtcgacgca aaggcaatcc tgagcgcaag 720
 actgagcaag agcagaagac tggaaaacct gatcgcacag ctgccgggag aaaagaagaa 780
 cggactgttc ggaaacctga tcgactgag cctgggactg acaccgaact tcaagagcaa 840
 cttcgacctg gcagaagacg caaagctgca gctgagcaag gacacatacg acgacgacct 900
 ggacaacctg ctggcacaga tcggagacca gtacgcagac ctgttcttgg cagcaaagaa 960
 cctgagcgac gcaatcctgc tgagcgacat cctgagagtc aacacagaaa tcacaaaggc 1020
 accgctgagc gcaagcatga tcaagagata cgacgaacac caccaggacc tgacactgct 1080
 gaaggcactg gtcagacagc agtgccgga aaagtacaag gaaatcttct tcgaccagag 1140
 caagaacgga tacgcaggat acatcgacgg aggagcaagc caggaagaat tctacaagtt 1200
 catcaagccg atcctggaaa agatggacgg aacagaagaa ctgctggtca agctgaacag 1260
 agaagacctg ctgagaaagc agagaacatt cgacaacgga agcatcccg accagatcca 1320
 cctgggagaa ctgcacgcaa tcctgagaag acaggaagac ttctaccctg tcctgaagga 1380
 caacagagaa aagatcgaag agatcctgac attcagaatc ccgtactacg tcggaccgct 1440
 ggcaagagga aacagcagat tcgcatggat gacaagaaag agcgaagaaa caatcacacc 1500
 gtggaacttc gaagaagtcg tcgacaaggg agcaagcgca cagagcttca tcgaaagaat 1560
 gacaaacttc gacaagaacc tgccgaacga aaaggtcctg ccgaagcaca gcctgctgta 1620
 cgaatacttc acagtctaca acgaactgac aaaggtcaag tacgtcacag aaggaatgag 1680
 aaagccggca ttcctgagcg gagaacagaa gaaggcaatc gtcgacctgc tgttcaagac 1740
 aaacagaaag gtcacagtca agcagctgaa ggaagactac ttcaagaaga tcgaatgctt 1800
 cgacagcgtc gaaatcagcg gagtgaaga cagattcaac gcaagcctgg gaacatacca 1860
 cgacctgctg aagatcatca aggacaagga cttcctggac aacgaagaaa acgaagacat 1920
 cctggaagac atcgtcctga cactgacact gttcgaagac agagaaatga tcgaagaaag 1980
 actgaagaca tacgcacacc tgttcgacga caaggtcatg aagcagctga agagaagaag 2040

atacacagga tggggaagac tgagcagaaa gctgatcaac ggaatcagag acaagcagag 2100
 cggaaagaca atcctggact tcctgaagag cgacggattc gcaaacagaa acttcatgca 2160
 gctgatccac gacgacagcc tgacattcaa ggaagacatc cagaaggcac aggtcagcgg 2220
 acaggagagac agcctgcacg aacacatcgc aaacctggca ggaagcccgg caatcaagaa 2280
 gggaatcctg cagacagtca aggtcgtcga cgaactggc aaggtcatgg gaagacacaa 2340
 gccggaaaac atcgtcatcg aaatggcaag agaaaaccag acaacacaga agggacagaa 2400
 gaacagcaga gaaagaatga agagaatcga agaaggaatc aaggaactgg gaagccagat 2460
 cctgaaggaa caccgggtcg aaaacacaca gctgcagaac gaaaagctgt acctgtacta 2520
 cctgcagaac ggaagagaca tgtacgtcga ccaggaactg gacatcaaca gactgagcga 2580
 ctacgacgtc gaccacatcg tcccgagag cttcctgaag gacgacagca tcgacaacaa 2640
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 cgtaagaag atgaagaact actggagaca gctgctgaac gcaaagctga tcacacagag 2760
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 attcatcaag agacagctgg tcgaaacaag acagatcaca aagcacgtcg cacagatcct 2880
 ggacagcaga atgaacacaa agtacgacga aaacgacaag ctgatcagag aagtcaaggt 2940
 catcacactg aagagcaagc tggtcagcga cttcagaaaag gacttccagt tctacaaggt 3000
 cagagaaatc aacaactacc accacgcaca cgacgcatac ctgaacgcag tcgtcggaac 3060
 agcactgatc aagaagtacc cgaagctgga aagcgaattc gtctacggag actacaaggt 3120
 ctacgacgtc agaaagatga tcgcaaagag cgaacaggaa atcggaagg caacagcaaa 3180
 gtacttcttc tacagcaaca tcatgaactt cttcaagaca gaaatcacac tggcaaacgg 3240
 agaaatcaga aagagaccgc tgatcgaaac aaacggagaa acaggagaaa tcgtctggga 3300
 caagggaaga gacttcgcaa cagtcagaaa ggtcctgagc atgccgcagg tcaacatcgt 3360
 caagaagaca gaagtcaga caggaggatt cagcaaggaa agcatcctgc cgaagagaaa 3420
 cagcgacaag ctgatcgcaa gaaagaagga ctgggacccg aagaagtacg gaggattcga 3480
 cagcccgaca gtcgcataca gcgtcctggc cgtcgcaaag gtcgaaaagg gaaagagcaa 3540
 gaagctgaag agcgtcaagg aactgctggg aatcacaatc atggaaagaa gcagcttcga 3600
 aaagaacccg atcgacttcc tggaagcaaa gggatacaag gaagtcaaga aggacctgat 3660
 catcaagctg ccgaagtaca gcctgttcga actggaaaac ggaagaaaga gaatgctggc 3720
 aagcgagga gaactgcaga agggaaacga actggcactg ccgagcaagt acgtcaactt 3780

cctgtacctg gcaagccact acgaaaagct gaaggggaagc ccggaagaca acgaacagaa 3840
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gacaaacctg ggagcaccgg cagcattcaa gtacttcgac acaacaatcg acagaaagag 4080
atacacaagc acaaaggaag tcctggacgc aacctgatc caccagagca tcacaggact 4140
gtacgaaaca agaatcgacc tgagccagct gggaggagac ggaggaggaa gcccgaagaa 4200
gaagagaaag gtctagctag ccatcacatt taaaagcatc tcagcctacc atgagaataa 4260
gagaaagaaa atgaagatca atagcttatt catctctttt tcttttcgt ttgtgtaaag 4320
ccaacaccct gtctaaaaaa cataaatttc ttaatcatt ttgcctcttt tctctgtgct 4380
tcaattaata aaaaatggaa agaacctcga g 4411

- <210> 257
- <211> 4481
- <212> ADN
- <213> Secuencia artificial

<220>
<223> Sintético: transcrito de Cas9 con 5 UTR de CMV, ORF correspondiente a la SEQ ID NO: 204, secuencia de Kozak, y 3 UTR de ALB

<400> 257
gggcagatcg cctggagacg ccatccacgc tgttttgacc tccatagaag acaccgggac 60
cgatccagcc tccgcggccg ggaacggtgc attggaacgc ggattccccg tgccaagagt 120
gactcaccgt ccttgacacg gccaccatgg acaagaagta cagcatcgga ctggacatcg 180
gaacaaacag cgtcggatgg gcagtcatca cagacgaata caaggtcccc agcaagaagt 240
tcaaggtcct gggaaacaca gacagacaca gcatcaagaa gaacctgatc ggagcactgc 300
tgttcgacag cggagaaaca gcagaagcaa caagactgaa gagaacagca agaagaagat 360
acacaagaag aaagaacaga atctgtctacc tgcaggaaat cttcagcaac gaaatggcaa 420
aggtcgacga cagcttcttc cacagactgg aagaaagctt cctggtcgaa gaagacaaga 480
agcacgaaag acacccgatc ttcggaaaca tcgtcgacga agtcgcatac cacgaaaagt 540
accgacaat ctaccacctg agaaagaagc tggtcgacag cacagacaag gcagacctga 600
gactgatcta cctggcactg gcacacatga tcaagttcag aggacacttc ctgatcgaag 660
gagacctgaa cccggacaac agcgacgtcg acaagctgtt catccagctg gtccagacat 720
acaaccagct gttcgaagaa aaccgatca acgcaagcgg agtcgacgca aaggcaatcc 780

tgagcgcaag actgagcaag agcagaagac tggaaaacct gatcgcacag ctgccgggag 840
aaaagaagaa cggactgttc ggaaacctga tcgcactgag cctgggactg acaccgaact 900
tcaagagcaa cttcgacctg gcagaagacg caaagctgca gctgagcaag gacacatacg 960
acgacgacct ggacaacctg ctggcacaga tcggagacca gtacgcagac ctgttcctgg 1020
cagcaaagaa cctgagcgac gcaatcctgc tgagcgacat cctgagagtc aacacagaaa 1080
tcacaaaggc accgctgagc gcaagcatga tcaagagata cgacgaacac caccaggacc 1140
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accagatcca cctgggagaa ctgcacgcaa tcctgagaag acaggaagac ttctaccctg 1440
tcctgaagga caacagagaa aagatcgaag agatcctgac attcagaatc ccgtactacg 1500
tcggaccgct ggcaagagga aacagcagat tcgcatggat gacaagaaag agcgaagaaa 1560
caatcacacc gtggaacttc gaagaagtcg tcgacaaggg agcaagcgca cagagcttca 1620
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tgttcaagac aaacagaaag gtcacagtca agcagctgaa ggaagactac ttcaagaaga 1860
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gaacatacca cgacctgtg aagatcatca aggacaagga cttctggac aacgaagaaa 1980
acgaagacat cctggaagac atcgtcctga cactgacact gttcgaagac agagaaatga 2040
tcgaagaaag actgaagaca tacgcacacc tgttcgacga caaggtcatg aagcagctga 2100
agagaagaag atacacagga tggggaagac tgagcagaaa gctgatcaac ggaatcagag 2160
acaagcagag cggaagaca atcctggact tcctgaagag cgacggattc gcaaacagaa 2220
acttcatgca gctgatccac gacgacagcc tgacattcaa ggaagacatc cagaaggcac 2280
aggtcagcgg acaggagac agcctgcacg aacacatcgc aaacctggca ggaagcccgg 2340
caatcaagaa gggaatcctg cagacagtca aggtcgtcga cgaactggtc aaggtcatgg 2400
gaagacacaa gccggaaaac atcgtcatcg aaatggcaag agaaaaccag acaacacaga 2460
agggacagaa gaacagcaga gaaagaatga agagaatcga agaaggaatc aaggaactgg 2520
gaagccagat cctgaaggaa caccggctcg aaaacacaca gctgcagaac gaaaagctgt 2580

acctgtacta cctgcagaac ggaagagaca tgtacgtcga ccaggaactg gacatcaaca 2640
gactgagcga ctacgacgtc gaccacatcg tcccgcagag cttcctgaag gacgacagca 2700
tcgacaacaa ggtcctgaca agaagcgaca agaacagagg aaagagcgac aacgtcccga 2760
gcgaagaagt cgtcaagaag atgaagaact actggagaca gctgctgaac gcaaagctga 2820
tcacacagag aaagttcgac aacctgacaa aggcagagag aggaggactg agcgaactgg 2880
acaaggcagg attcatcaag agacagctgg tcgaaacaag acagatcaca aagcacgtcg 2940
cacagatcct ggacagcaga atgaacacaa agtacgacga aaacgacaag ctgatcagag 3000
aagtcaaggt catcacactg aagagcaagc tggtcagcga cttcagaaag gacttccagt 3060
tctacaaggt cagagaaatc aacaactacc accacgcaca cgacgcatac ctgaacgcag 3120
tcgtcggaa acgactgatc aagaagtacc cgaagctgga aagcgaattc gtctacggag 3180
actacaaggt ctacgacgtc agaaagtga tcgcaaagag cgaacaggaa atcggaagg 3240
caacagcaaa gtacttcttc tacagcaaca tcatgaactt cttcaagaca gaaatcacac 3300
tggcaaacgg agaaatcaga aagagaccgc tgatcgaaac aaacggagaa acaggagaaa 3360
tcgtctggga caagggaaga gacttcgcaa cagtcagaaa ggtcctgagc atgccgcagg 3420
tcaacatcgt caagaagaca gaagtccaga caggaggatt cagcaaggaa agcatcctgc 3480
cgaagagaaa cagcgacaag ctgatcgcaa gaaagaagga ctgggacccg aagaagtacg 3540
gaggattcga cagcccga gtcgcataca gcgtcctggt cgtcgcaaag gtcgaaaagg 3600
gaaagagcaa gaagctgaag agcgtcaagg aactgctggg aatcacaatc atggaaagaa 3660
gcagcttcga aaagaacccg atcgacttcc tggaagcaaa gggatacaag gaagtcaaga 3720
aggacctgat catcaagctg ccgaagtaca gcctgttcga actggaaaac ggaagaaaga 3780
gaatgctggc aagcgcagga gaactgcaga agggaaacga actggcactg ccgagcaagt 3840
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acgaacagaa gcagctgttc gtcgaacagc acaagcacta cctggacgaa atcatcgaac 3960
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acagaaagag atacacaagc acaaaggaag tcctggacgc aacctgatc caccagagca 4200
tcacaggact gtacgaaaca agaatcgacc tgagccagct gggaggagac ggaggaggaa 4260
gcccgaagaa gaagagaaag gtctagctag ccatcacatt taaaagcatc tcagcctacc 4320

atgagaataa gagaaagaaa atgaagatca atagcttatt catctctttt tctttttcgt 4380
tgggtgtaaag ccaacaccct gtctaaaaaa cataaatttc tttaatcatt ttgcctcttt 4440
tctctgtgct tcaattaata aaaaatggaa agaacctga g 4481

<210> 258
<211> 4348
<212> ADN
<213> Secuencia artificial

<220>
<223> Sintético: transcrito de Cas9 con 5 UTR de HBB, ORF correspondiente a la
SEQ ID NO: 204, secuencia de Kozak, y 3 UTR de HBB

<400> 258
gggacatttg cttctgacac aactgtgttc actagcaacc tcaaacagac accggatctg 60
ccaccatgga caagaagtac agcatcggac tggacatcgg aacaacagc gtcggatggg 120
cagtcacac agacgaatac aaggtccga gcaagaagtt caaggtcctg ggaaacacag 180
acagacacag catcaagaag aacctgatcg gagcactgct gttcgacagc ggagaaacag 240
cagaagcaac aagactgaag agaacagcaa gaagaagata cacaagaaga aagaacagaa 300
tctgtacct gcaggaaatc ttcagcaacg aaatggcaaa ggtcgacgac agcttcttcc 360
acagactgga agaaagcttc ctggtcgaag aagacaagaa gcacgaaaga caccgatct 420
tcggaaacat cgtcgacgaa gtcgcatacc acgaaaagta cccgacaatc taccacctga 480
gaaagaagct ggtcgacagc acagacaagg cagacctgag actgatctac ctggcactgg 540
cacacatgat caagttcaga ggacacttcc tgatcgaagg agacctgaac ccggacaaca 600
gcgacgtcga caagctgttc atccagctgg tccagacata caaccagctg ttcgaagaaa 660
acccgatcaa cgcaagcggg gtcgacgcaa aggcaatcct gagcgcaaga ctgagcaaga 720
gcagaagact ggaaaacctg atcgacagc tgccgggaga aaagaagaac ggactgttcg 780
gaaacctgat cgactgagc ctgggactga caccgaactt caagagcaac ttcgacctgg 840
cagaagacgc aaagctgcag ctgagcaagg acacatacga cgacgacctg gacaacctgc 900
tggcacagat cggagaccag tacgagacc tgttcctggc agcaaagaac ctgagcgacg 960
caatcctgct gagcgacatc ctgagagtca acacagaaat cacaaggca ccgctgagcg 1020
caagcatgat caagagatac gacgaacacc accaggacct gacactgctg aaggcactgg 1080
tcagacagca gctgccggaa aagtacaagg aaatcttctt cgaccagagc aagaacggat 1140
acgcaggata catcgacgga ggagcaagcc aggaagaatt ctacaagttc atcaagccga 1200
tcctggaaaa gatggacgga acagaagaac tgctgggtcaa gctgaacaga gaagacctgc 1260

tgagaaagca gagaacattc gacaacggaa gcatcccgca ccagatccac ctgggagaac 1320
 tgcacgcaat cctgagaaga caggaagact tctacccgtt cctgaaggac aacagagaaa 1380
 agatcgaana gatactgaca ttcagaatcc cgtactacgt cggaccgctg gcaagaggaa 1440
 acagcagatt cgcattgatg acaagaaaga gcgaagaaac aatcacaccg tggaacttcg 1500
 aagaagtcgt cgacaaggga gcaagcgac agagcttcat cgaaagaatg aaaaacttcg 1560
 acaagaacct gccgaacgaa aaggtcctgc cgaagcacag cctgctgtac gaatacttca 1620
 cagtctaca cgaactgaca aaggtcaagt acgtcacaga aggaatgaga aagccggcat 1680
 tcctgagcgg agaacagaag aaggcaatcg tcgacctgct gttcaagaca aacagaaaagg 1740
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 agatcatcaa ggacaaggac ttctggaca acgaagaaaa cgaagacatc ctggaagaca 1920
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 acgcacacct gttcgacgac aaggtcatga agcagctgaa gagaagaaga tacacaggat 2040
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agaagtaccc gaagctggaa agcgaattcg tctacggaga ctacaaggtc tacgacgtca 3120
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agagaccgct gatcgaaca aacggagaaa caggagaaat cgtctgggac aagggaagag 3300
acttcgaac agtcagaaag gtctgagca tgccgcaggt caacatcgtc aagaagacag 3360
aagtccagac aggaggattc agcaaggaaa gcatcctgcc gaagagaaac agcgacaagc 3420
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acaagccgat cagagaacag gcagaaaaca tcatccacct gttcactg acaaacctgg 4020
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caaaggaagt cctggacgca acactgatcc accagagcat cacaggactg tacgaaacaa 4140
gaatcgacct gagccagctg ggaggagacg gaggaggaag cccgaagaag aagagaaagg 4200
tctagctagc gctcgcttct ttgctgtcca atttctatta aaggttcctt tgttcctaa 4260
gtccaactac taaactgggg gatattatga agggccttga gcatctggat tctgcctaat 4320
aaaaaacatt tattttcatt gcctcgag 4348

<210> 259
<211> 4325
<212> ADN
<213> Secuencia artificial

<220>
<223> Sintético: transcrito de Cas9 con 5 UTR de XBG, ORF correspondiente a la
SEQ ID NO: 204, secuencia de Kozak, y 3 UTR de XBG

<400> 259
gggaagctca gaataaacgc tcaactttgg ccggatctgc caccatggac aagaagtaca 60
gcatcggact ggacatcgga acaaacagcg tcggatgggc agtcacaca gacgaataca 120

aggtcccag caagaagttc aaggtcctgg gaaacacaga cagacacagc atcaagaaga 180
 acctgatcgg agcactgctg ttcgacagcg gagaacacagc agaagcaaca agactgaaga 240
 gaacagcaag aagaagatac acaagaagaa agaacagaat ctgctacctg caggaaatct 300
 tcagcaacga aatggcaaag gtcgacgaca gcttcttcca cagactggaa gaaagcttcc 360
 tggtcgaaga agacaagaag cacgaaagac acccgatctt cggaacatc gtcgacgaag 420
 tcgcatacca cgaaaagtac ccgacaatct accacctgag aaagaagctg gtcgacagca 480
 cagacaaggc agacctgaga ctgatctacc tggcactggc acacatgac aagttcagag 540
 gacacttct gatcgaagga gacctgaacc cggacaacag cgacgtcgac aagctgttca 600
 tccagctggt ccagacatac aaccagctgt tcgaagaaaa cccgatcaac gcaagcggag 660
 tcgacgcaa ggcaatcctg agcgcaagac tgagcaagag cagaagactg gaaaacctga 720
 tcgcacagct gccgggagaa aagaagaacg gactgttcgg aaacctgac gcactgagcc 780
 tgggactgac accgaacttc aagagcaact tcgacctggc agaagacgca aagctgcagc 840
 tgagcaagga cacatacgac gacgacctgg acaacctgct ggcacagac ggagaccagt 900
 acgcagacct gttcctggca gcaaagaacc tgagcgacgc aatcctgctg agcgacatcc 960
 tgagagtcaa cacagaaatc acaaaggcac cgctgagcgc aagcatgac aagagatacg 1020
 acgaacacca ccaggacctg aactgctga aggcactggt cagacagcag ctgccggaaa 1080
 agtacaagga aatcttcttc gaccagagca agaacggata cgaggatac atcgacggag 1140
 gagcaagcca ggaagaattc tacaagtca tcaagccgat cctggaaaag atggacggaa 1200
 cagaagaact gctggtcaag ctgaacagag aagacctgct gagaaagcag agaacattcg 1260
 acaacggaag catccgcac cagatccacc tgggagaact gcacgcaatc ctgagaagac 1320
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 tcagaatccc gtactacgtc ggaccgtgg caagaggaaa cagcagattc gcatggatga 1440
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 caagcgaca gagcttcac gaaagaatga caaacttga caagaacctg ccgaacgaaa 1560
 aggtcctgcc gaagcacagc ctgctgtac aatacttcac agtctacaac gaactgaca 1620
 aggtcaagta cgtcacagaa ggaatgagaa agccggcatt cctgagcgga gaacagaaga 1680
 aggcaatcgt cgacctgctg ttcaagaca acagaaaggt cacagtcaag cagctgaagg 1740
 aagactactt caagaagatc gaatgcttcg acagcgtcga aatcagcgga gtcgaagaca 1800
 gattcaacgc aagcctggga acataccacg acctgctgaa gatcatcaag gacaaggact 1860

tcctggacaa cgaagaaaac gaagacatcc tggaagacat cgtcctgaca ctgacactgt 1920

tcgaagacag agaaatgac gaagaaagac tgaagacata cgacacactg ttcgacgaca 1980

aggtcatgaa gcagctgaag agaagaagat acacaggatg ggggaagactg agcagaaaagc 2040

tgatcaacgg aatcagagac aagcagagcg gaaagacaat cctggacttc ctgaagagcg 2100

acggattcgc aaacagaaaac ttatgcagc tgatccacga cgacagcctg acattcaagg 2160

aagacatcca gaaggcacag gtcagcggac agggagacag cctgcacgaa cacatcgcaa 2220

acctggcagg aagcccgga atcaagaagg gaatcctgca gacagtcaag gtcgtcgacg 2280

aactggtcaa ggtcatggga agacacaagc cggaaaacat cgtcatcgaa atggcaagag 2340

aaaaccagac aacacagaag ggacagaaga acagcagaga aagaatgaag agaatcgaag 2400

aaggaatcaa ggaactggga agccagatcc tgaaggaaca cccggtcgaa aacacacagc 2460

tgagaacga aaagctgtac ctgtactacc tgagaacgg aagagacatg tacgtcgacc 2520

aggaactgga catcaacaga ctgagcgact acgacgtcga ccacatcgtc ccgagagct 2580

tcctgaagga cgacagcatc gacaacaagg tcctgacaag aagcgacaag aacagaggaa 2640

agagcgacaa cgtcccgagc gaagaagtgc tcaagaagat gaagaactac tggagacagc 2700

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acgacaagct gatcagagaa gtcaaggtca tcacactgaa gagcaagctg gtcagcgact 2940

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acgcatacct gaacgcagtc gtcggaacag cactgatcaa gaagtaccg aagctggaaa 3060

gcgaattcgt ctacggagac tacaaggtct acgacgtcag aaagatgac gcaaagagcg 3120

aacaggaaat cggaaggca acagcaaagt acttcttcta cagcaacatc atgaacttct 3180

tcaagacaga aatcacactg gcaaacggag aaatcagaaa gagaccgctg atcgaacaa 3240

acggagaaac aggagaaatc gtctgggaca agggaagaga cttcgcaaca gtcagaaagg 3300

tcctgagcat gccgcaggtc aacatcgtca agaagacaga agtccagaca ggaggattca 3360

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tcgcaaaggt cgaaaaggga aagagcaaga agctgaagag cgtcaaggaa ctgctgggaa 3540

tcacaatcat ggaaagaagc agcttcgaaa agaaccgat cgacttctg gaagcaaagg 3600

gatacaagga agtcaagaag gacctgatca tcaagtgcc gaagtacagc ctgttcgaac 3660

tggaaaacgg aagaaagaga atgctggcaa ggcgaggaga actgcagaag ggaaacgaac 3720
tggcactgcc gagcaagtac gtcaacttcc tgtacctggc aagccactac gaaaagctga 3780
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gaggagacgg aggaggaagc ccgaagaaga agagaaaggt ctagctagca ccagcctcaa 4200
gaacacccga atggagtctc taagtacat aataccaact tacactttac aaaatgttgt 4260
ccccaaaat gtagccattc gtatctgctc ctaataaaaa gaaagtttct tcacattctc 4320

tcgag 4325

<210> 260
<211> 4325
<212> ADN
<213> Secuencia artificial

<220>
<223> Sintético: transcrito de Cas9 con AGG como los primeros tres nucleótidos
para el uso con CleanCap™, 5 UTR de XBG, ORF correspondiente a la SEQ
ID NO: 204, secuencia de Kozak, y 3 UTR de XBG

<400> 260
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gcatcggact ggacatcgga acaaacagcg tcggatgggc agtcatcaca gacgaataca 120

aggtcccag caagaagttc aaggtcctgg gaaacacaga cagacacagc atcaagaaga 180

acctgatcgg agcactgctg ttcgacagcg gagaacagc agaagcaaca agactgaaga 240

gaacagcaag aagaagatac acaagaagaa agaacagaat ctgctacctg caggaaatct 300

tcagcaacga aatggcaaag gtcgacgaca gcttcttcca cagactggaa gaaagcttcc 360

tggtcgaaga agacaagaag cacgaaagac acccgatctt cggaacatc gtcgacgaag 420

tcgcatacca cgaaaagtac ccgacaatct accacctgag aaagaagctg gtcgacagca 480

cagacaaggc agacctgaga ctgatctacc tggcactggc acacatgatc aagttcagag 540

gacacttct gatcgaagga gacctgaacc cggacaacag cgacgtcgac aagctgttca 600

tccagctggt ccagacatac aaccagctgt tcgaagaaaa cccgatcaac gcaagcggag 660

tcgacgcaaa ggcaatcctg agcgcaagac tgagcaagag cagaagactg gaaaacctga	720
tcgcacagct gccgggagaa aagaagaacg gactgttcgg aaacctgac gactgagcc	780
tgggactgac accgaacttc aagagcaact tcgacctggc agaagacgca aagctgcagc	840
tgagcaagga cacatacgac gacgacctgg acaacctgct ggcacagatc ggagaccagt	900
acgcagacct gttcctggca gcaaagaacc tgagcgacgc aatcctgctg agcgacatcc	960
tgagagtcaa cacagaaatc acaaaggcac cgctgagcgc aagcatgac aagagatacg	1020
acgaacacca ccaggacctg acactgctga aggcactggt cagacagcag ctgccgaaa	1080
agtacaagga aatcttcttc gaccagagca agaacggata cgaggatac atcgacggag	1140
gagcaagcca ggaagaattc tacaagttca tcaagccgat cctggaaaag atggacggaa	1200
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acaacggaag catccgcac cagatccacc tgggagaact gcacgcaatc ctgagaagac	1320
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caagaaagag cgaagaaaca atcacaccgt ggaacttga agaagtcgtc gacaaggag	1500
caagcgaca gagttcatc gaaagaatga caaacttga caagaacctg ccgaacgaaa	1560
aggtcctgcc gaagcacagc ctgctgtacg aatacttcac agtctacaac gaactgaca	1620
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aggcaatcgt cgacctgtg ttcaagaca acagaaaggc cacagtcaag cagctgaagg	1740
aagactactt caagaagatc gaatgcttcg acagcgtcga aatcagcgga gtcgaagaca	1800
gattcaacgc aagcctggga acataccacg acctgtgaa gatcatcaag gacaaggact	1860
tcctggaca cgaagaaaac gaagacatcc tggaagacat cgtcctgaca ctgacactgt	1920
tcgaagacag agaatgac gaagaaagac tgaagacata cgacacctg ttcgacgaca	1980
aggtcatgaa gcagctgaag agaagaagat acacaggatg gggaagactg agcagaaagc	2040
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acggattcgc aaacagaaac ttcatgcagc tgatccacga cgacagcctg acattcaagg	2160
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aaggaatcaa ggaactggga agccagatcc tgaaggaaca cccggtcgaa aacacacagc	2460

tgcaaacga aaagctgtac ctgtactacc tgcaaacgg aagagacatg tacgtcgacc 2520
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tggcactgcc gagcaagtac gtcaacttc tgtacctggc aagccactac gaaaagctga 3780
agggaagccc ggaagacaac gaacagaagc agctgttcgt cgaacagcac aagcactacc 3840
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cactgatcca ccagagcatc acaggactgt acgaaacaag aatcgacctg agccagctgg 4140
gaggagacgg aggaggaagc ccgaagaaga agagaaaggt ctagctagca ccagcctcaa 4200

gaacacccga atggagtctc taagctacat aataccaact tacactttac aaaatgttgt 4260

ccccaaaat gtagccattc gtatctgctc ctaataaaaa gaaagtttct tcacattctc 4320

tcgag 4325

- <210> 261
 - <211> 4411
 - <212> ADN
 - <213> Secuencia artificial
- <220>
- <223> Sintético: transcrito de Cas9 con AGG como los primeros tres nucleótidos para el uso con CleanCap™, 5 UTR de HSD, ORF correspondiente a la SEQ ID NO: 204, secuencia de Kozak, y 3 UTR de ALB

<400> 261

agggtcccga gtcggcgctc agcggctctg cttgttcgtg tgtgtgtcgt tgcaggcctt 60

attcggatcc gccaccatgg acaagaagta cagcatcgga ctggacatcg gaacaaacag 120

cgtcggatgg gcagtcatca cagacgaata caaggtcccg agcaagaagt tcaaggtcct 180

gggaaacaca gacagacaca gcatcaagaa gaacctgac ggagcactgc tgttcgacag 240

cggagaaaca gcagaagcaa caagactgaa gagaacagca agaagaagat acacaagaag 300

aaagaacaga atctgctacc tgcaggaaat cttcagcaac gaaatggcaa aggtcgacga 360

cagcttctc cacagactgg aagaaagctt cctggtcgaa gaagacaaga agcacgaaag 420

acacccgatc ttggaaaca tcgtcgacga agtcgcatac cacgaaaagt acccgacaat 480

ctaccacctg agaaagaagc tggtcgacag cacagacaag gcagacctga gactgatcta 540

cctggcactg gcacacatga tcaagttcag aggacacttc ctgatcgaag gagacctgaa 600

cccggacaac agcgacgtcg acaagctgtt catccagctg gtccagacat acaaccagct 660

gttcgaagaa aacccgatca acgcaagcgg agtcgacgca aaggcaatcc tgagcgcaag 720

actgagcaag agcagaagac tggaaaacct gatcgcacag ctgccgggag aaaagaagaa 780

cggactgttc ggaaacctga tcgcactgag cctgggactg acaccgaact tcaagagcaa 840

cttcgacctg gcagaagacg caaagctgca gctgagcaag gacacatacg acgacgacct 900

ggacaacctg ctggcacaga tcggagacca gtacgcagac ctgttctctg cagcaaagaa 960

cctgagcgac gcaatcctgc tgagcgacat cctgagagtc aacacagaaa tcacaaaggc 1020

accgtgagc gcaagcatga tcaagagata cgacgaacac caccaggacc tgacactgct 1080

gaaggcactg gtcagacagc agtgccgga aaagtacaag gaaatcttct tcgaccagag 1140

caagaacgga tacgcaggat acatcgacgg aggagcaagc caggaagaat tctacaagtt 1200

catcaagccg atcctggaaa agatggacgg aacagaagaa ctgctggtca agctgaacag 1260

agaagacctg ctgagaaagc agagaacatt cgacaacgga agcatccgc accagatcca 1320
 cctgggagaa ctgcacgcaa tctgagaag acaggaagac ttctaccgt tctgaagga 1380
 caacagagaa aagatcgaaa agatcctgac attcagaatc ccgtactacg tcggaccgct 1440
 ggcaagagga aacagcagat tcgcatggat gacaagaaag agcgaagaaa caatcacacc 1500
 gtggaacttc gaagaagtcg tcgacaaggg agcaagcgca cagagcttca tcgaaagaat 1560
 gacaaacttc gacaagaacc tgccgaacga aaaggtcctg ccgaagcaca gcctgctgta 1620
 cgaatacttc acagtctaca acgaactgac aaaggtcaag tacgtcacag aaggaatgag 1680
 aaagccggca ttcctgagcg gagaacagaa gaaggcaatc gtcgacctgc tgttcaagac 1740
 aaacagaaag gtcacagtca agcagctgaa ggaagactac ttcaagaaga tcgaatgctt 1800
 cgacagcgtc gaaatcagcg gagtgaaga cagattcaac gcaagcctgg gaacatacca 1860
 cgacctgctg aagatcatca aggacaagga cttcctggac aacgaagaaa acgaagacat 1920
 cctggaagac atcgtcctga cactgacact gttcgaagac agagaaatga tcgaagaaag 1980
 actgaagaca tacgcacacc tgttcgacga caaggtcatg aagcagctga agagaagaag 2040
 atacacagga tggggaagac tgagcagaaa gctgatcaac ggaatcagag acaagcagag 2100
 cggaaagaca atcctggact tctgaagag cgacggattc gcaaacagaa acttcatgca 2160
 gctgatccac gacgacagcc tgacattcaa ggaagacatc cagaaggcac aggtcagcgg 2220
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 gggaatcctg cagacagtca aggtcgtcga cgaactggc aaggtcatgg gaagacacaa 2340
 gccggaaaac atcgtcatcg aaatggcaag agaaaaccag acaacacaga agggacagaa 2400
 gaacagcaga gaaagaatga agagaatcga agaaggaatc aaggaactgg gaagccagat 2460
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 ggtcctgaca agaagcgaca agaacagagg aaagagcgac aacgtcccga gcgaagaagt 2700
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 attcatcaag agacagctgg tcgaaacaag acagatcaca aagcacgtcg cacagatcct 2880
 ggacagcaga atgaacacaa agtacgacga aaacgacaag ctgatcagag aagtcaaggt 2940
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cagagaaatc aacaactacc accacgcaca cgacgcatac ctgaacgcag tcgtcggaac 3060
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ctacgacgtc agaaagatga tcgcaaagag cgaacaggaa atcggaaagg caacagcaaa 3180
gtacttcttc tacagcaaca tcatgaactt cttcaagaca gaaatcacac tggcaaacgg 3240
agaaatcaga aagagaccgc tgatcgaaac aaacggagaa acaggagaaa tcgtctggga 3300
caagggaaga gacttcgcaa cagtcagaaa ggtcctgagc atgccgcagg tcaacatcgt 3360
caagaagaca gaagtccaga caggaggatt cagcaaggaa agcatcctgc cgaagagaaa 3420
cagcgacaag ctgatcgcaa gaaagaagga ctgggacccg aagaagtacg gaggattcga 3480
cagcccgaca gtcgcataca gcgtcctggt cgtcgcaaag gtcgaaaagg gaaagagcaa 3540
gaagtgaag agcgtcaagg aactgtctggg aatcacaatc atggaaagaa gcagcttcga 3600
aaagaacccg atcgacttcc tggaagcaaa gggatacaag gaagtcaaga aggacctgat 3660
catcaagctg ccgaagtaca gcctgttcga actggaaaac ggaagaaaga gaatgtctggc 3720
aagcgagga gaactgcaga agggaaacga actggcactg ccgagcaagt acgtcaactt 3780
cctgtacttg gcaagccact acgaaaagct gaagggaagc ccggaagaca acgaacagaa 3840
gcagctgttc gtcgaacagc acaagcacta cctggacgaa atcatcgaac agatcagcga 3900
attcagcaag agagtcatcc tggcagacgc aaacctggac aaggtcctga gcgcatacaa 3960
caagcacaga gacaagccga tcagagaaca ggcagaaaac atcatccacc tgttcacact 4020
gacaaacctg ggagcaccgg cagcattcaa gtacttcgac acaacaatcg acagaaagag 4080
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gaagagaaag gtctagctag ccatcacatt taaaagcatc tcagcctacc atgagaataa 4260
gagaaagaaa atgaagatca atagcttatt catctctttt tcttttctgt tgggtgaaag 4320
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tcaattaata aaaaatggaa agaacctcga g 4411

<210> 262

<400> 262
000

<210> 263
<211> 93
<212> ADN
<213> Secuencia artificial

<220>
<223> Sintético: secuencia poli-A 100

<400> 263
aaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 60

aaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaa 93

<210> 264
<211> 44
<212> ADN
<213> Secuencia artificial

<220>
<223> Sintético: ARN de guía única G209 dirigido al gen TTR de ratón

<400> 264
aaataagaga gaaaagaaga gtaagaagaa atataagagc cacc 44

<210> 265
<211> 3312
<212> ADN
<213> Secuencia artificial

<220>
<223> Sintético: ORF que codifica Cas9 de Neisseria meningitidis que usa codones de mínima uridina, con codones de inicio y parada

<400> 265
atggcagcat tcaagccgaa ctcatcaac tacatcctgg gactggacat cggaatcgca 60

tcggtcggat gggcaatggt cgaaatcgac gaagaagaaa acccgatcag actgatcgac 120

ctgggagtca gagtcttcga aagagcagaa gtcccgaaga caggagactc gctggcaatg 180

gcaagaagac tggcaagatc ggtcagaaga ctgacaagaa gaagagcaca cagactgctg 240

agaacaagaa gactgctgaa gagagaagga gtctgcagg cagcaaactt cgacgaaaac 300

ggactgatca agtcgctgcc gaacacaccg tggcagctga gagcagcagc actggacaga 360

aagctgacac cgctggaatg gtcggcagtc ctgctgcacc tgatcaagca cagaggatac 420

ctgtcgaga gaaagaacga aggagaaaca gcagacaagg aactgggagc actgctgaag 480

ggagtcgcag gaaacgcaca cgactgcag acaggagact tcagaacacc ggcagaactg 540

gcactgaaca agttcgaaaa ggaatcgga cacatcagaa accagagatc ggactactcg 600

cacacattct cgagaaagga cctgcaggca gaactgatcc tgctgttcga aaagcagaag 660

gaattcggaa accgcacgt ctggggagga ctgaaggaag gaatcgaaac actgctgatg 720

acacagagac cggcactgtc gggagacgca gtccagaaga tgctgggaca ctgcacattc 780

gaaccggcag aaccgaaggc agcaaagaac acatacacag cagaaagatt catctggctg 840

acaaagctga acaacctgag aatcctggaa cagggatcgg aaagaccgct gacagacaca 900
gaaagagcaa cactgatgga cgaaccgtac agaaagtcga agctgacata cgcacaggca 960
agaaagctgc tgggactgga agacacagca ttcttcaagg gactgagata cggaaaggac 1020
aacgcagaag catcgacact gatggaaatg aaggcatacc acgcaatctc gagagcactg 1080
gaaaaggaag gactgaagga caagaagtcg ccgctgaacc tgtcgccgga actgcaggac 1140
gaaatcggaa cagcattctc gctgttcaag acagacgaag acatcacagg aagactgaag 1200
gacagaatcc agccggaaat cctggaagca ctgctgaagc acatctcgtt cgacaagttc 1260
gtccagatct cgctgaaggc actgagaaga atcgtcccg cgtatggaaca gggaaagaga 1320
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aagatctacc tgccgccgat cccggcagac gaaatcagaa acccggtcgt cctgagagca 1440
ctgtcgagg caagaaaggt catcaacgga gtcgtcagaa gatacggatc gccggcaaga 1500
atccacatcg aaacagcaag agaagtcgga aagtcgttca aggacagaaa ggaaatcgaa 1560
aagagacagg aagaaaacag aaaggacaga gaaaaggcag cagcaaagtt cagagaatac 1620
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cagcagcacg gaaagtcct gtactcgga aaggaaatca acctgggaag actgaacgaa 1740
aagggatacg tcgaaatcga ccacgactg ccgttctcga gaacatggga cgactcgttc 1800
aacaacaagg tcctgtcct gggatcggaa aaccagaaca agggaaacca gacaccgtac 1860
gaatacttca acggaagga caactcgaga gaatggcagg aattcaaggc aagagtcgaa 1920
acatcgagat tcccagatc gaagaagcag agaatcctgc tgcagaagtt cgacgaagac 1980
ggattcaagg aaagaaacct gaacgacaca agatactca acagattcct gtgccagttc 2040
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cagatcacia acctgtgag aggattctgg ggactgagaa aggtcagagc agaaaacgac 2160
agacaccacg cactggacgc agtcgtcgtc gcatgctcga cagtcgcaat gcagcagaag 2220
atcacaagat tcgtcagata caaggaaatg aacgcattcg acggaagac aatcgacaag 2280
gaaacaggag aagtcctgca ccagaagaca cacttcccgc agccgtggga attcttcgca 2340
caggaagtca tgatcagagt cttcggaag ccggacggaa agccggaatt cgaagaagca 2400
gacacactgg aaaagctgag aacactgctg gcagaaaagc tgtcgtcag accggaagca 2460
gtccacgaat acgtcacacc gctgttcgtc tcgagagcac cgaacagaaa gatgtcggga 2520
caggacaca tggaacagt caagtcggca aagagactgg acgaaggagt ctcggtcctg 2580
agagtccgc tgacacagct gaagctgaag gacctggaaa agatggtcaa cagagaaaga 2640

gaaccgaagc tgtacgaagc actgaaggca agactggaag cacacaagga cgacccggca 2700
aaggcattcg cagaaccgtt ctacaagtac gacaaggcag gaaacagaac acagcaggtc 2760
aaggcagtca gagtcaaca ggtccagaag acaggagtct gggtcagaaa ccacaacgga 2820
atcgagaca acgaacaat ggtcagagta gacgtcttcg aaaagggaga caagtactac 2880
ctggtccga tctactcgtg gcaggtcgca aagggaatcc tgccggacag agcagtcgtc 2940
cagggaaagg acgaagaaga ctggcagctg atcgacgact cgttcaactt caagttctcg 3000
ctgcacccga acgacctggt cgaagtcac acaaagaagg caagaatgtt cggatacttc 3060
gcatcgtgcc acagaggaac aggaacatc aacatcagaa tccacgacct ggaccacaag 3120
atcgaaaga acggaatcct ggaaggaatc ggagtcaaga cagcactgtc gttccagaag 3180
taccagatcg acgaactggg aaaggaaatc agaccgtgca gactgaagaa gagaccgccg 3240
gtcagatccg gaaagagaac agcagacgga tcggaattcg aatcgccgaa gaagaagaga 3300
aagtcgaat ga 3312

- <210> 266
- <211> 3306
- <212> ADN
- <213> Secuencia artificial
- <220>
- <223> Sintético: ORF que codifica Cas9 de Neisseria meningitidis que usa codones de mínima uridina (sin codones de inicio y parada; adecuado para su inclusión en la secuencia de codificación de proteínas de fusión)

<400> 266
gcagcattca agccgaactc gatcaactac atcctgggac tggacatcgg aatcgcatcg 60
gtcggatggg caatggtcga aatcgacgaa gaagaaaacc cgatcagact gatcgacctg 120
ggagtcagag tcttcgaaag agcagaagtc ccgaagacag gagactcgct ggcaatggca 180
agaagactgg caagatcggc cagaagactg acaagaagaa gagcacacag actgctgaga 240
acaagaagac tgctgaagag agaaggagtc ctgcaggcag caaacttcga cgaaaacgga 300
ctgatcaagt cgctgccgaa cacacctggc cagctgagag cagcagcact ggacagaaag 360
ctgacaccgc tggaatggtc ggagtcctg ctgcacctga tcaagcacag aggatacctg 420
tcgcagagaa agaacgaagg agaaacagca gacaaggaac tgggagcact gctgaaggga 480
gtcgcaggaa acgcacacgc actgcagaca ggagacttca gaacaccggc agaactggca 540
ctgaacaagt tcgaaaagga atcgggacac atcagaaacc agagatcgga ctactcgac 600
acattctcga gaaaggacct gcaggcagaa ctgacctgc tgttcgaaaa gcagaaggaa 660

ttcggaaacc cgcacgtctc gggaggactg aaggaaggaa tcgaaacact gctgatgaca 720
 cagagaccgg cactgtcggg agacgcagtc cagaagatgc tgggacactg cacattcgaa 780
 ccggcagaac cgaaggcagc aaagaacaca tacacagcag aaagattcat ctggctgaca 840
 aagctgaaca acctgagaat cctggaacag ggatcggaaa gaccgctgac agacacagaa 900
 agagcaacac tgatggacga accgtacaga aagtcgaagc tgacatacgc acaggcaaga 960
 aagctgctgg gactggaaga cacagcattc ttcaaggac tgagatacgg aaaggacaac 1020
 gcagaagcat cgacactgat ggaaatgaag gcataccacg caatctcgag agcactggaa 1080
 aaggaaggac tgaaggacaa gaagtcgccg ctgaacctgt cgccggaact gcaggacgaa 1140
 atcggaaacag cattctcgct gttcaagaca gacgaagaca tcacaggaag actgaaggac 1200
 agaatccagc cggaaatcct ggaagcactg ctgaagcaca tctcgttcga caagttcgtc 1260
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 gacgaagcat gcgcagaaat ctacggagac cactacggaa agaagaacac agaagaaaag 1380
 atctacctgc cgccgatccc ggcagacgaa atcagaaacc cggtcgtcct gagagcactg 1440
 tcgcaggcaa gaaaggtcat caacggagtc gtcagaagat acggatcgcc ggcaagaatc 1500
 cacatcgaac cagcaagaga agtcggaaag tcgttcaagg acagaaagga aatcgaagaa 1560
 agacaggaag aaaacagaaa ggacagagaa aaggcagcag caaagttcag agaatacttc 1620
 ccgaacttcg tcggagaacc gaagtcgaag gacatcctga agctgagact gtacgaacag 1680
 cagcacggaa agtgctgtga ctcgggaaag gaaatcaacc tgggaagact gaacgaaaag 1740
 ggatacgtcg aaatcgacca cgactgccg ttctcgagaa catgggacga ctcgttcaac 1800
 aacaaggctc tggctctggg atcggaaaac cagaacaagg gaaaccagac accgtacgaa 1860
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 ttcaaggaaa gaaacctgaa cgacacaaga tacgtcaaca gattcctgtg ccagttcgtc 2040
 gcagacagaa tgagactgac aggaaaggga aagaagagag tcttcgcatc gaacggacag 2100
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 caccacgcac tggacgcagt cgtcgtcgca tgctcgacag tcgcaatgca gcagaagatc 2220
 acaagattcg tcagatacaa ggaaatgaac gcattcgacg gaaagacaat cgacaaggaa 2280
 acaggagaag tctgcacca gaagacacac ttcccgcagc cgtgggaatt cttgcacag 2340
 gaagtcatga tcagagtctt cggaagccg gacggaaagc cggaattcga agaagcagac 2400
 aactggaaa agctgagaac actgtggca gaaaagctgt cgtcgagacc ggaagcagtc 2460

cacgaatacg tcacaccgct gttcgtctcg agagcaccga acagaaagat gtcgggacag 2520
ggacacatgg aaacagtcaa gtcggcaaag agactggacg aaggagtctc ggtcctgaga 2580
gtcccgtga cacagctgaa gctgaaggac ctggaaaaga tggtaacag agaaagagaa 2640
ccgaagctgt acgaagcact gaaggcaaga ctggaagcac acaaggacga cccggcaaag 2700
gcattcgag aaccgttcta cagtacgac aaggcaggaa acagaacaca gcaggtcaag 2760
gcagtcagag tcgaacaggt ccagaagaca ggagtctggg tcagaaacca caacggaatc 2820
gcagacaacg caacaatggt cagagtagac gtcttcgaaa agggagacaa gtactacctg 2880
gtcccgatct actcgtggca ggtcgcaaag ggaatcctgc cggacagagc agtcgtccag 2940
ggaaaggacg aagaagactg gcagctgac gacgactct tcaactcaa gttctcgtg 3000
caccgaacg acctggtcga agtcatcaca aagaaggcaa gaatgttcgg atacttcgca 3060
tcgtgccaca gaggaacagg aaacatcaac atcagaatcc acgacctgga ccacaagatc 3120
ggaaagaacg gaatcctgga aggaatcgga gtcaagacag cactgtcgtt ccagaagtac 3180
cagatcgacg aactgggaaa ggaaatcaga ccgtgcagac tgaagaagag accgccggtc 3240
agatccggaa agagaacagc agacggatcg gaattcgaat cgccgaagaa gaagagaaag 3300
gtcgaa 3306

<210> 267
<211> 3636
<212> ADN
<213> Secuencia artificial

<220>
<223> Sintético: transcrito que comprende la SEQ ID NO: 265 (que codifica Cas9 de
Neisseria meningitidis)

<400> 267
gggagaccca agctggctag cgtttaaact taagcttgga tccgccacca tggcagcatt 60
caagccgaac tcgatcaact acatcctggg actggacatc ggaatcgcac cggtcggatg 120
ggcaatggtc gaaatcgacg aagaagaaaa ccgcatcaga ctgatcgacc tgggagtcag 180
agtcttcgaa agagcagaag tcccgaagac aggagactcg ctggcaatgg caagaagact 240
ggcaagatcg gtcagaagac tgacaagaag aagagcacac agactgctga gaacaagaag 300
actgctgaag agagaaggag tcctgcaggc agcaaacttc gacgaaaacg gactgatcaa 360
gtcgtgccg aacacaccgt ggagctgag agcagcagca ctggacagaa agctgacacc 420
gctggaatgg tcggcagtc tgctgcacct gatcaagcac agaggatacc tgtcgagag 480
aaagaacgaa ggagaaacag cagacaagga actgggagca ctgctgaagg gactcgagg 540

aaacgcacac gcactgcaga caggagactt cagaacaccg gcagaactgg cactgaacaa 600
 gttcgaaaag gaatcgggac acatcagaaa ccagagatcg gactactcg acacattctc 660
 gagaaaggac ctgcaggcag aactgatcct gctgttcgaa aagcagaagg aattcggaaa 720
 cccgcacgtc tcgggaggac tgaaggaagg aatcgaaaca ctgctgatga cacagagacc 780
 ggcaactgtc ggagacgcag tccagaagat gctgggacac tgcacattcg aaccggcaga 840
 accgaaggca gcaaagaaca catacacagc agaaagattc atctggctga caaagctgaa 900
 caacctgaga atcctggaac agggatcgga aagaccgtg acagacacag aaagagcaac 960
 actgatggac gaaccgtaca gaaagtcgaa gctgacatac gcacaggcaa gaaagctgct 1020
 gggactggaa gacacagcat tttcaaggg actgagatac ggaaaggaca acgcagaagc 1080
 atcgacactg atggaaatga aggcatacca cgcaatctc agagcactgg aaaaggaagg 1140
 actgaaggac aagaagtcgc cgctgaacct gtcgccgga ctgcaggacg aaatcggaac 1200
 agcattctc ctgttcaaga cagacgaaga catcacagga agactgaagg acagaatcca 1260
 gccggaaatc ctggaagcac tgctgaagca catctcgtt gacaagttc tccagatctc 1320
 gctgaaggca ctgagaagaa tcgtcccgct gatggaacag ggaaagagat acgacgaagc 1380
 atgcgcagaa atctacggag accactacgg aaagaagaac acagaagaaa agatctacct 1440
 gccgccgatc ccggcagacg aaatcagaaa cccggtcgtc ctgagagcac tgtcgaggc 1500
 aagaaaggtc atcaacggag tcgtcagaag atacggatcg ccggcaagaa tccacatcga 1560
 aacagcaaga gaagtcggaa agtcgttcaa ggacagaaag gaaatcgaaa agagacagga 1620
 agaaaacaga aaggacagag aaaaggcagc agcaaagttc agagaatact tcccgaactt 1680
 cgtcggagaa ccgaagtcga aggacatcct gaagctgaga ctgtacgaac agcagcacgg 1740
 aaagtcctg tactcgggaa aggaaatcaa cctgggaaga ctgaacgaaa agggatacgt 1800
 cgaaatcgac cacgcactgc cgttctcgag aacatgggac gactcgttca acaacaaggt 1860
 cctggtcctg ggatcggaaa accagaacaa gggaaccag acaccgtacg aatacttcaa 1920
 cggaaaggac aactcgagag aatggcagga attcaaggca agagtcgaaa catcgagatt 1980
 cccgagatcg aagaagcaga gaatcctgct gcagaagttc gacgaagacg gattcaagga 2040
 aagaaacctg aacgacacaa gatactcaa cagattcctg tgccagttc tcgcagacag 2100
 aatgagactg acaggaaagg gaaagaagag agtcttcgca tcgaacggac agatcacaaa 2160
 cctgtgaga ggattctggg gactgagaaa ggtcagagca gaaaacgaca gacaccacgc 2220
 actggacgca gtcgtcgtc catgctcgac agtcgcaatg cagcagaaga tcacaagatt 2280

cgtcagatac aaggaaatga acgcattcga cggaaagaca atcgacaagg aaacaggaga 2340
agtcctgcac cagaagacac acttcccga gccgtgggaa ttcttcgcac aggaagtcac 2400
gatcagagtc ttcggaaagc cggacggaaa gccggaattc gaagaagcag acacactgga 2460
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gtacgaagca ctgaaggcaa gactggaagc acacaaggac gaccggcaa aggcattcgc 2760
agaaccgttc tacaagtacg acaaggcagg aaacagaaca cagcaggtca aggcagtcag 2820
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cgaagaagac tggcagctga tcgacgactc gttcaacttc aagttctgc tgcacccgaa 3060
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cggaatcctg gaaggaatcg gactcaagac agcactgtcg ttccagaagt accagatcga 3240
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atagctagct cgagtctaga gggcccgttt aaaccgctg atcagcctcg actgtcctt 3420
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atagcaggca tgctggggat gcggtgggct ctatgg 3636

<210> 268
<211> 1103
<212> PRT
<213> Secuencia artificial

<220>
<223> Sintético: secuencia de aminoácidos de Cas9 de Neisseria meningitidis

<400> 268

Met Ala Ala Phe Lys Pro Asn Ser Ile Asn Tyr Ile Leu Gly Leu Asp
1 5 10 15

Ile Gly Ile Ala Ser Val Gly Trp Ala Met Val Glu Ile Asp Glu Glu
20 25 30

Glu Asn Pro Ile Arg Leu Ile Asp Leu Gly Val Arg Val Phe Glu Arg
35 40 45

Ala Glu Val Pro Lys Thr Gly Asp Ser Leu Ala Met Ala Arg Arg Leu
50 55 60

Ala Arg Ser Val Arg Arg Leu Thr Arg Arg Arg Ala His Arg Leu Leu
65 70 75 80

Arg Thr Arg Arg Leu Leu Lys Arg Glu Gly Val Leu Gln Ala Ala Asn
85 90 95

Phe Asp Glu Asn Gly Leu Ile Lys Ser Leu Pro Asn Thr Pro Trp Gln
100 105 110

Leu Arg Ala Ala Ala Leu Asp Arg Lys Leu Thr Pro Leu Glu Trp Ser
115 120 125

Ala Val Leu Leu His Leu Ile Lys His Arg Gly Tyr Leu Ser Gln Arg
130 135 140

Lys Asn Glu Gly Glu Thr Ala Asp Lys Glu Leu Gly Ala Leu Leu Lys
145 150 155 160

Gly Val Ala Gly Asn Ala His Ala Leu Gln Thr Gly Asp Phe Arg Thr
165 170 175

Pro Ala Glu Leu Ala Leu Asn Lys Phe Glu Lys Glu Ser Gly His Ile
180 185 190

Arg Asn Gln Arg Ser Asp Tyr Ser His Thr Phe Ser Arg Lys Asp Leu
195 200 205

Gln Ala Glu Leu Ile Leu Leu Phe Glu Lys Gln Lys Glu Phe Gly Asn
210 215 220

Pro His Val Ser Gly Gly Leu Lys Glu Gly Ile Glu Thr Leu Leu Met
225 230 235 240

Thr Gln Arg Pro Ala Leu Ser Gly Asp Ala Val Gln Lys Met Leu Gly

245	250	255
His Cys Thr Phe Glu Pro Ala Glu Pro Lys Ala Ala Lys Asn Thr Tyr		
260	265	270
Thr Ala Glu Arg Phe Ile Trp Leu Thr Lys Leu Asn Asn Leu Arg Ile		
275	280	285
Leu Glu Gln Gly Ser Glu Arg Pro Leu Thr Asp Thr Glu Arg Ala Thr		
290	295	300
Leu Met Asp Glu Pro Tyr Arg Lys Ser Lys Leu Thr Tyr Ala Gln Ala		
305	310	315 320
Arg Lys Leu Leu Gly Leu Glu Asp Thr Ala Phe Phe Lys Gly Leu Arg		
325	330	335
Tyr Gly Lys Asp Asn Ala Glu Ala Ser Thr Leu Met Glu Met Lys Ala		
340	345	350
Tyr His Ala Ile Ser Arg Ala Leu Glu Lys Glu Gly Leu Lys Asp Lys		
355	360	365
Lys Ser Pro Leu Asn Leu Ser Pro Glu Leu Gln Asp Glu Ile Gly Thr		
370	375	380
Ala Phe Ser Leu Phe Lys Thr Asp Glu Asp Ile Thr Gly Arg Leu Lys		
385	390	395 400
Asp Arg Ile Gln Pro Glu Ile Leu Glu Ala Leu Leu Lys His Ile Ser		
405	410	415
Phe Asp Lys Phe Val Gln Ile Ser Leu Lys Ala Leu Arg Arg Ile Val		
420	425	430
Pro Leu Met Glu Gln Gly Lys Arg Tyr Asp Glu Ala Cys Ala Glu Ile		
435	440	445
Tyr Gly Asp His Tyr Gly Lys Lys Asn Thr Glu Glu Lys Ile Tyr Leu		
450	455	460
Pro Pro Ile Pro Ala Asp Glu Ile Arg Asn Pro Val Val Leu Arg Ala		
465	470	475 480

Leu Ser Gln Ala Arg Lys Val Ile Asn Gly Val Val Arg Arg Tyr Gly
485 490 495

Ser Pro Ala Arg Ile His Ile Glu Thr Ala Arg Glu Val Gly Lys Ser
500 505 510

Phe Lys Asp Arg Lys Glu Ile Glu Lys Arg Gln Glu Glu Asn Arg Lys
515 520 525

Asp Arg Glu Lys Ala Ala Ala Lys Phe Arg Glu Tyr Phe Pro Asn Phe
530 535 540

Val Gly Glu Pro Lys Ser Lys Asp Ile Leu Lys Leu Arg Leu Tyr Glu
545 550 555 560

Gln Gln His Gly Lys Cys Leu Tyr Ser Gly Lys Glu Ile Asn Leu Gly
565 570 575

Arg Leu Asn Glu Lys Gly Tyr Val Glu Ile Asp His Ala Leu Pro Phe
580 585 590

Ser Arg Thr Trp Asp Asp Ser Phe Asn Asn Lys Val Leu Val Leu Gly
595 600 605

Ser Glu Asn Gln Asn Lys Gly Asn Gln Thr Pro Tyr Glu Tyr Phe Asn
610 615 620

Gly Lys Asp Asn Ser Arg Glu Trp Gln Glu Phe Lys Ala Arg Val Glu
625 630 635 640

Thr Ser Arg Phe Pro Arg Ser Lys Lys Gln Arg Ile Leu Leu Gln Lys
645 650 655

Phe Asp Glu Asp Gly Phe Lys Glu Arg Asn Leu Asn Asp Thr Arg Tyr
660 665 670

Val Asn Arg Phe Leu Cys Gln Phe Val Ala Asp Arg Met Arg Leu Thr
675 680 685

Gly Lys Gly Lys Lys Arg Val Phe Ala Ser Asn Gly Gln Ile Thr Asn
690 695 700

Leu Leu Arg Gly Phe Trp Gly Leu Arg Lys Val Arg Ala Glu Asn Asp
705 710 715 720

Arg His His Ala Leu Asp Ala Val Val Val Ala Cys Ser Thr Val Ala
725 730 735

Met Gln Gln Lys Ile Thr Arg Phe Val Arg Tyr Lys Glu Met Asn Ala
740 745 750

Phe Asp Gly Lys Thr Ile Asp Lys Glu Thr Gly Glu Val Leu His Gln
755 760 765

Lys Thr His Phe Pro Gln Pro Trp Glu Phe Phe Ala Gln Glu Val Met
770 775 780

Ile Arg Val Phe Gly Lys Pro Asp Gly Lys Pro Glu Phe Glu Glu Ala
785 790 795 800

Asp Thr Leu Glu Lys Leu Arg Thr Leu Leu Ala Glu Lys Leu Ser Ser
805 810 815

Arg Pro Glu Ala Val His Glu Tyr Val Thr Pro Leu Phe Val Ser Arg
820 825 830

Ala Pro Asn Arg Lys Met Ser Gly Gln Gly His Met Glu Thr Val Lys
835 840 845

Ser Ala Lys Arg Leu Asp Glu Gly Val Ser Val Leu Arg Val Pro Leu
850 855 860

Thr Gln Leu Lys Leu Lys Asp Leu Glu Lys Met Val Asn Arg Glu Arg
865 870 875 880

Glu Pro Lys Leu Tyr Glu Ala Leu Lys Ala Arg Leu Glu Ala His Lys
885 890 895

Asp Asp Pro Ala Lys Ala Phe Ala Glu Pro Phe Tyr Lys Tyr Asp Lys
900 905 910

Ala Gly Asn Arg Thr Gln Gln Val Lys Ala Val Arg Val Glu Gln Val
915 920 925

Gln Lys Thr Gly Val Trp Val Arg Asn His Asn Gly Ile Ala Asp Asn
930 935 940

Ala Thr Met Val Arg Val Asp Val Phe Glu Lys Gly Asp Lys Tyr Tyr
945 950 955 960

Leu Val Pro Ile Tyr Ser Trp Gln Val Ala Lys Gly Ile Leu Pro Asp
965 970 975

Arg Ala Val Val Gln Gly Lys Asp Glu Glu Asp Trp Gln Leu Ile Asp
980 985 990

Asp Ser Phe Asn Phe Lys Phe Ser Leu His Pro Asn Asp Leu Val Glu
995 1000 1005

Val Ile Thr Lys Lys Ala Arg Met Phe Gly Tyr Phe Ala Ser Cys
1010 1015 1020

His Arg Gly Thr Gly Asn Ile Asn Ile Arg Ile His Asp Leu Asp
1025 1030 1035

His Lys Ile Gly Lys Asn Gly Ile Leu Glu Gly Ile Gly Val Lys
1040 1045 1050

Thr Ala Leu Ser Phe Gln Lys Tyr Gln Ile Asp Glu Leu Gly Lys
1055 1060 1065

Glu Ile Arg Pro Cys Arg Leu Lys Lys Arg Pro Pro Val Arg Ser
1070 1075 1080

Gly Lys Arg Thr Ala Asp Gly Ser Glu Phe Glu Ser Pro Lys Lys
1085 1090 1095

Lys Arg Lys Val Glu
1100

<210> 269
<211> 100
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: ARN de guía única G390 dirigido al gen TTR de rata

<220>
<221> base_modificada
<222> (1)..(3)
<223> Enlace PS, nucleótido 2'-O-Me

<220>
<221> base_modificada
<222> (29)..(40)

<223> nucleótido 2'-O-Me

<220>
<221> base_modificada
<222> (69)..(96)
<223> nucleótido 2'-O-Me

<220>
<221> base_modificada
<222> (97)..(100)
<223> Enlace PS, nucleótido 2'-O-Me

<400> 269
gccgagucug gagagcugca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 270
<211> 74
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: ARNtr

<400> 270
aacagcauag caaguuaaaa uaaggcuagu ccguuaucaa cuugaaaaag uggcaccgag 60

ucggugcuuu uuuu 74

<210> 271

<400> 271
000

<210> 272
<211> 100
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: ARN de guía única G534 dirigido al gen TTR de rata

<220>
<221> base_modificada
<222> (1)..(3)
<223> Enlace PS, nucleótido 2'-O-Me

<220>
<221> base_modificada
<222> (29)..(40)
<223> nucleótido 2'-O-Me

<220>
<221> base_modificada
<222> (69)..(96)

<223> nucleótido 2'-O-Me

<220>
<221> base_modificada
<222> (97)..(100)
<223> Enlace PS, nucleótido 2'-O-Me

<400> 272
acgcaauau caguccagcg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 273
<211> 95
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: secuencia modificada de ARNsg G000395 inactiva truncada 5'

<220>
<221> base_modificada
<222> (1)..(3)
<223> Enlace PS, nucleótido 2'-O-Me

<220>
<221> base_modificada
<222> (24)..(35)
<223> nucleótido 2'-O-Me

<220>
<221> base_modificada
<222> (64)..(91)
<223> nucleótido 2'-O-Me

<220>
<221> base_modificada
<222> (92)..(95)
<223> Enlace PS, nucleótido 2'-O-Me

<400> 273
gcaauggugu agcggguuuu agagcuagaa auagcaagu aaaaauaaggc uaguccguua 60

ucaacuugaa aaaguggcac cgagucggug cuuuu 95

<210> 274
<211> 7
<212> PRT
<213> Secuencia artificial

<220>
<223> Sintético: NLS de SV40

<400> 274

Pro Lys Lys Lys Arg Lys Val

<400> 278
gccgccrcca ugg 13