

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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SEQ ID NO: 205 que usa codones con expresión generalmente alta en humanos

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 <210> 29
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 <223> Sintético: ARNg CR003359 dirigido a TTR humana (Exón 3)

 <400> 29
 agugagucug gagagcugca 20

 <210> 30
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 <223> Sintético: ARNg CR003360 dirigido a TTR humana (Exón 3)

<400> 30
gugagucugg agagcugcau 20

<210> 31
<211> 20
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<213> Secuencia artificial

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<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
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 <213> Secuencia artificial

 <220>
 <223> Sintético: ARNg CR003367 dirigido a TTR humana (Exón 3)

 <400> 37
 agacaccaa 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
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 <213> Secuencia artificial

 <220>
 <223> Sintético: ARNg CR003369 dirigido a TTR humana (Exón 3)

<400> 39
cucugcaugc ucauggaug 20

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

<220>
<223> Sintético: ARNg CR003370 dirigido a TTR humana (Exón 3)

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ccucugcaug cucauggaau 20

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<213> Secuencia artificial

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

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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)

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 gcggcggggg ccggagucgu 20

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

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

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 <210> 46
 <211> 20
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 <213> Secuencia artificial

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

 <400> 46
 cggcaauggu guagcggcgg 20

 <210> 47
 <211> 20
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 <213> Secuencia artificial

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

 <400> 47
 gcggcaaugg uguagcggcg 20

 <210> 48
 <211> 20
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 <220>
 <223> Sintético: ARNg CR003378 dirigido a TTR humana (Exón 4)

<400> 48
ggcgggcaaug guguagcggc 20

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

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

<400> 49
gggcgggcaau gguguagcgg 20

<210> 50
<211> 20
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<213> Secuencia artificial

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

<400> 50
gcagggcggc aaugguguag 20

<210> 51
<211> 20
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<213> Secuencia artificial

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

<400> 51
ggggcucagc agggcggcaa 20

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

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

<400> 52
ggaguagggg cucagcaggg 20

<210> 53
<211> 20

<212> ARN
 <213> Secuencia artificial

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

 <400> 53
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 <210> 54
 <211> 20
 <212> ARN
 <213> Secuencia artificial

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

 <400> 54
 aaaggagua 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
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 <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
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<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 acucaccgua 20

 <210> 66
 <211> 20
 <212> ARN
 <213> Secuencia artificial

 <220>
 <223> Sintético: ARNg CR005301 dirigido a TTR humana (Exón 1)

<400> 66
gucacagaaa cacucaccgu 20

<210> 67
<211> 20
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: ARNg CR005302 dirigido a TTR humana (Exón 2)

<400> 67
acgugucuuc ucuacacca 20

<210> 68
<211> 20
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: ARNg CR005303 dirigido a TTR humana (Exón 2)

<400> 68
ugaauccaag uguccucuga 20

<210> 69
<211> 20
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: ARNg CR005304 dirigido a TTR humana (Exón 2)

<400> 69
ggccgugcau guguucagaa 20

<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
 aaauuuuuuu 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

000

<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>
<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> 87
aaaggcugcu gaugacaccu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60
cguuaucaac 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>
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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> 88
 ucuagaacuu ugaccaucag guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60
 cguuaucaac 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>
 <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> 89
 uguagaaggg auauacaaag guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60
 cguuaucaac 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>

<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> 90

uccacucauu cuuggcagga guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 91

<211> 100

<212> ARN

<213> Secuencia artificial

<220>

<223> Sintético: secuencia modificada de ARNsg G000484 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> 91

agacaccaa ucuuacugga guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 92

<211> 100

<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

<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> 92

ccuccucugc cuugcuggac guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 93

<211> 100

<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>

<221> base_modificada

<222> (97)..(100)

<223> Enlace PS, nucleótido 2'-O-Me

<400> 93

acacaaauac caguccagca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 94

<211> 100

<212> ARN

<213> Secuencia artificial

<220>

<223> Sintético: secuencia modificada de ARNsg G000487 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
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<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
aaaguucug augcuguccg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguaaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 96
<211> 100
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: secuencia modificada de ARNsg G000489 dirigido a TTR humana

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<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> 96
uuugaccauc agaggacacu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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

<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
<222> (69)..(96)
<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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cguaaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 98
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<212> ARN
<213> Secuencia artificial

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

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

<220>
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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> 98
auaccagucc agcaaggcag guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60
cguaaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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

<220>
<223> Sintético: secuencia modificada de ARNsg G000492 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

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<223> Enlace PS, nucleótido 2'-O-Me

<400> 99

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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> 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> 100

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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu

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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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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<223> Enlace PS, nucleótido 2'-O-Me

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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

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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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 <223> Enlace PS, nucleótido 2'-O-Me

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 <223> Enlace PS, nucleótido 2'-O-Me

 <400> 109
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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

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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

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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 gcttcctggt cgaagaagac aagaagcacg aaagacaccc gatcttcgga	360
aacatcgtcg acgaagtcgc ataccacgaa aagtaccga caatctacca cctgagaaag	420
aagctggctg acagcacaga caaggcagac ctgagactga tctacctggc actggcacac	480
atgatcaagt tcagaggaca cttcctgata gaaggagacc tgaacccgga caacagcgac	540
gtcgacaagc tggtcatcca gctgggtccag acatacaacc agctgttcga agaaaacccg	600
atcaacgcaa gcggagtcga cgcaaaggca atcctgagcg caagactgag caagagcaga	660
agactggaaa acctgatcg acagctgccg ggagaaaaga agaacggact gttcggaac	720
ctgatcgac tgagcctggg actgacaccg aacttcaaga gcaacttcga 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 cggaagagta caaggaaatc ttcttcgacc agagcaagaa cggatacgca	1080
ggatacatcg acggaggagc aagccaggaa gaattctaca agttcatcaa gccgatcctg	1140
gaaaagatgg acggaacaga agaactgctg gtcaagctga acagagaaga cctgctgaga	1200
aagcagagaa cattcgacaa cggaagcatc ccgcaccaga tccacctggg agaactgcac	1260
gcaatcctga gaagacagga agacttctac ccgttcctga aggacaacag agaaaagatc	1320
gaaaagatcc tgacattcag aatcccgtac tacgtcggac cgctggcaag aggaaacagc	1380
agattcgcat ggatgacaag aaagagcgaa gaaacaatca caccgtggaa cttcgaagaa	1440
gtcgtcgaca agggagcaag cgcacagagc ttcacgaaa gaatgacaaa cttcgacaag	1500
aacctgccga acgaaaaggc cctgccgaag cacagcctgc tgtacgaata cttcacagtc	1560
tacaacgaac tgacaaaggc caagtacgtc acagaaggaa tgagaaagcc ggcattcctg	1620
agcggagaa acagaaggc aatcgtcgac ctgctgttca agacaaacag aaaggtcaca	1680
gtcaagcagc tgaaggaaga ctacttcaag aagatcgaat gcttcgacag cgtcgaaatc	1740
agcggagtcg aagacagatt caacgcaagc ctgggaacat accacgacct gctgaagatc	1800

atcaaggaca	aggacttcct	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
gacttcctga	agagcgacgg	attcgcaaac	agaaacttca	tgcagctgat	ccacgacgac	2100
agcctgacat	tcaaggaaga	catccagaag	gcacaggtca	gcggaacagg	agacagcctg	2160
cacgaacaca	tcgcaaacct	ggcaggaagc	ccggcaatca	agaagggaat	cctgcagaca	2220
gtcaagggtc	tcgacgaact	ggtcaaggtc	atgggaagac	acaagccgga	aaacatcgtc	2280
atcgaaatgg	caagagaaaa	ccagacaaca	cagaagggac	agaagaacag	cagagaaaaga	2340
atgaagagaa	tcgaagaagg	aatcaaggaa	ctgggaagcc	agatcctgaa	ggaacacccg	2400
gtcgaaaaca	cacagctgca	gaacgaaaag	ctgtacctgt	actacctgca	gaacggaaga	2460
gacatgtacg	tcgaccagga	actggacatc	aacagactga	gcgactacga	cgtcgaccac	2520
atcgtcccg	agagcttcct	gaaggacgac	agcatcgaca	acaaggtcct	gacaagaagc	2580
gacaagaaca	gaggaaagag	cgacaacgtc	ccgagcgaag	aagtcgtcaa	gaagatgaag	2640
aactactgga	gacagctgct	gaacgcaaag	ctgatcacac	agagaaagtt	cgacaacctg	2700
acaaaggcag	agagaggagg	actgagcgaa	ctggacaagg	caggattcat	caagagacag	2760
ctggctgaaa	caagacagat	cacaaagcac	gtcgcacaga	tcctggacag	cagaatgaac	2820
acaaagtacg	acgaaaacga	caagctgata	agagaagtca	aggtcatcac	actgaagagc	2880
aagctggtca	gcgacttcag	aaaggacttc	cagttctaca	aggtcagaga	aatcaacaac	2940
taccaccacg	cacacgacgc	atacctgaac	gcagtcgtcg	gaacagcact	gatcaagaag	3000
tacccgaagc	tggaaagcga	attcgtctac	ggagactaca	aggtctacga	cgtcagaaaag	3060
atgatcgcaa	agagcgaaca	ggaaatcgga	aaggcaacag	caaagtactt	cttctacagc	3120
aacatcatga	acttcttcaa	gacagaaatc	acactggcaa	acggagaaat	cagaaagaga	3180
ccgctgatcg	aaacaaacgg	agaaacagga	gaaatcgtct	gggacaaggg	aagagacttc	3240
gcaacagtca	gaaaggctct	gagcatgccg	caggtcaaca	tcgtcaagaa	gacagaagtc	3300
cagacaggag	gattcagcaa	ggaaagcatc	ctgccgaaga	gaaacagcga	caagctgata	3360
gcaagaaaga	aggactggga	cccgaagaag	tacggaggat	tcgacagccc	gacagtcgca	3420

tacagcgtcc tggctcgtcg aaaggtcgaa aagggaaaga gcaagaagct gaagagcgtc	3480
aaggaactgc tgggaatcac aatcatggaa agaagcagct tcgaaaagaa cccgatcgac	3540
ttcctggaag caaaggata caaggaagtc aagaaggacc tgatcatcaa gctgccgaag	3600
tacagcctgt tcgaactgga aaacggaaga aagagaatgc tggcaagcgc aggagaactg	3660
cagaaggga acgaactggc actgccgagc aagtacgtca acttcctgta cctggcaagc	3720
cactacgaaa agctgaaggg aagcccggaa gacaacgaac agaagcagct gttcgtcgaa	3780
cagcacaagc actacctgga cgaaatcatc gaacagatca gcgaattcag caagagagtc	3840
atcctggcag acgcaaact ggacaaggtc ctgagcgcac acaacaagca cagagacaag	3900
ccgatcagag aacaggcaga aaacatcatc cacctgttca cactgacaaa cctgggagca	3960
ccggcagcat tcaagtactt cgacacaaca atcgacagaa agagatacac aagcacaag	4020
gaagtcctgg 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 aagttcaagg tcctggggaa caccgataga	120
cacagcatca agaaaaatct catcggagcc ctgctgtttg actccggcga aaccgcagaa	180
gcgacccggc tcaaacttac cgcgaggcga cgctacaccc ggcggaagaa tcgcatctgc	240
tatctgcaag agatcttttc gaacgaaatg gcaaaggtcg acgacagctt cttccaccgc	300
ctggaagaat ctttcctggt ggaggaggac aagaagcatg aacggcatcc tatctttgga	360
aacatcgtcg acgaagtggc gtaccacgaa aagtaccga ccatctacca tctgcggaag	420
aagttggttg actcaactga caaggccgac ctgagattga tctacttggc cctcgcccat	480
atgatcaaat tccgcggaca cttcctgac gaaggcgatc tgaaccctga taactccgac	540

gtggataagc ttttcattca actggtgcag acctacaacc aactgttcga agaaaaccca	600
atcaatgcta gcggcgctga tgccaaggcc atcctgtccg cccggctgtc gaagtcgcgg	660
cgcttcgaaa acctgatcgc acagctgccg ggagagaaaa agaacggact tttcggaac	720
ttgatcgtc tctcactggg actcactccc aatttcaagt ccaattttga cctggccgag	780
gacgcgaagc tgcaactctc aaaggacacc tacgacgacg acttggacaa tttgctggca	840
caaattggcg atcagtacgc ggatctgttc cttgccgcta agaacctttc ggacgcaatc	900
ttgctgtccg atatcctgcg cgtgaacacc gaaataacca aagcgccgct tagcgcctcg	960
atgattaagc ggtacgacga gcatcaccag gatctcacgc tgctcaaagc gctcgtgaga	1020
cagcaactgc ctgaaaagta caaggagatc ttcttcgacc agtccaagaa tgggtacgca	1080
gggtacatcg atggaggcgc tagccaggaa gagttctata agttcatcaa gccaatcctg	1140
gaaaagatgg acggaaccga agaactgctg gtcaagctga acaggaggga tctgctccgg	1200
aaacagagaa cttttgacaa cggatccatt ccccaccaga tccatctggg tgagctgcac	1260
gccatcttgc ggcgccagga ggacttttac ccattcctca aggacaaccg ggaaaagatc	1320
gagaaaattc tgacgttccg catcccgtat tacgtgggcc cactggcgcg cggcaattcg	1380
cgcttcgcgt ggatgactag aaaatcagag gaaaccatca ctcttgga tttcgaggaa	1440
gttgtggata agggagcttc ggcacaaagc ttcacgaac gaatgaccaa cttcgacaag	1500
aatctcccaa acgagaaggt gcttcctaag cacagcctcc ttacgaata cttcactgtc	1560
tacaacgaac tgactaaagt gaaatacggt actgaaggaa tgaggaagcc ggcctttctg	1620
tccggagaac agaagaaagc aattgtcgat ctgctgttca agaccaaccg caaggtgacc	1680
gtcaagcagc ttaaagagga ctacttcaag aagatcgagt gtttcgactc agtggaaatc	1740
agcgggggtgg aggacagatt caacgcttcg ctgggaacct atcatgatct cctgaagatc	1800
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catctcttcg acgataaggt catgaaacaa ctcaagcgcc gccggtacac tggttggggc	1980
cgctctccc gcaagctgat caacggtatt cgcgataaac agagcggtaa aactatcctg	2040
gatttcctca aatcggatgg cttcgcta atcgtaacttca tgcaattgat ccacgacgac	2100
agcctgacct ttaaggagga catccaaaaa gcacaagtgt ccggacaggg agactcactc	2160

catgaacaca	tcgcgaatct	ggccggttcg	ccggcgatta	agaagggaat	tctgcaaact	2220
gtgaaggtgg	tcgacgagct	ggtgaaggtc	atgggacggc	acaaaccgga	gaatatcgtg	2280
attgaaatgg	cccagaaaaa	ccagactacc	cagaagggcc	agaaaaactc	ccgcgaaagg	2340
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aacatcatga	actttttcaa	gactgaaatt	acgctggcca	atggagaaat	caggaagagg	3180
ccactgatcg	aaactaacgg	agaaacgggc	gaaatcgtgt	gggacaaggg	cagggacttc	3240
gcaactgttc	gcaaagtgtc	ctctatgccg	caagtcaata	ttgtgaagaa	aaccgaagtg	3300
caaaccggcg	gattttcaaa	ggaatcgatc	ctcccaaaga	gaaatagcga	caagctcatt	3360
gcacgcaaga	aagactggga	cccgaagaag	tacggaggat	tcgattcgcc	gactgtcgca	3420
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caaaaaggaa	atgagctggc	cttgccatgc	aagtacgtca	acttcctcta	tcttgcttcg	3720
cactacgaaa	aactcaaagg	gtcaccggaa	gataacgaac	agaagcagct	tttcgtggag	3780

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cagcacaagc attatctgga tgaaatcatc gaacaaatct ccgagttttc aaagcgcgtg      3840
atcctcgccg acgccaacct cgacaaagtc ctgtcggcct acaataagca tagagataag      3900
ccgatcagag aacaggccga gaacattatc cacttgttca ccctgactaa cctgggagcc      3960
ccagccgcct tcaagtactt cgatactact atcgatcgca aaagatacac gtccaccaag      4020
gaagttctgg acgcgaccct gatccaccaa agcatcactg gactctacga aactaggatc      4080
gatctgtcgc agctgggtgg cgatggcggt ggatctccga aaaagaagag aaaggtgtaa      4140
tga                                                                           4143

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

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

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<400> 203

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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
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 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 aaauacaaggu 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 aacuucaaga 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 caaggaauc 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	caccguggaa	cuucgaagaa	1440
gucgucgaca	aggagcaag	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	caacggaau	agagacaagc	agagcggaaa	gacaauccug	2040
gacuuccuga	agagcgacgg	auucgcaa	agaaacuuca	ugcagcugau	ccacgacgac	2100
agccugacau	ucaaggaaga	cauccagaag	gcacagguca	gcggacaggg	agacagccug	2160
cacgaacaca	ucgcaaaccu	ggcaggaagc	ccggcaauca	agaagggaau	ccugcagaca	2220
gucaaggucg	ucgacgaacu	ggucaagguc	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
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	cacaaagcac	gucgcacaga	uccuggacag	cagaaugaac	2820
acaaaguacg	acgaaaacga	caagcugauc	agagaaguca	aggucaucac	acugaagagc	2880

aagcugguca gcgacuucag aaaggacuuc caguucuaca aggucagaga aaUCAaacaac	2940
uaccaccacg cacacgacgc auaccugaac gcagucgucg gaacagcacu gaucaagaag	3000
uacccgaagc uggaaagcga auucgucuac ggagacuaca agguacuacga cgucagaaag	3060
augaucgcaa agagcgaaca ggaaaucgga aaggcaacag caaaguacuu cuucuacagc	3120
aacaucauga acuucuuaa gacagaaauc acacuggcaa acggagaaaau cagaaagaga	3180
ccgcugaucg aaacaaacgg agaaacagga gaaaucgucu 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 uggucgucgc aaaggucgaa aagggaaga gcaagaagcu gaagagcguc	3480
aaggaacugc ugggaauac aaauaggaa agaagcagcu ucgaaaagaa cccgaucgac	3540
uuccuggaag caaagggaua caaggaaguc aagaaggacc ugaucaucaa gcugccgaag	3600
uacagccugu ucgaacugga aaacggaaga aagagaaugc uggcaagcgc aggagaacug	3660
cagaagggaa acgaacuggc acugccgagc aaguacguca acuuccugua ccuggcaagc	3720
cacuacgaaa agcugaaggg aagcccggaa gacaacgaac agaagcagcu guucgucgaa	3780
cagcacaagc acuaccugga cgaaaaucauc 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 agcuggggagg 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	aauacaaagu	gccguccaag	aaguucaagg	uccuggggaa	caccgauaga	120
cacagcauca	agaaaaaucu	caucggagcc	cugcuguuug	acuccggcga	aaccgcagaa	180
gcgacccggc	ucaaacguac	cgcgaggcga	cgcuacaccc	ggcggaagaa	ucgcaucugc	240
uaucugcaag	agaucuuuuc	gaacgaaaug	gcaaaggucg	acgacagcuu	cuuccaccgc	300
cuggaagaau	cuuuccuggu	ggaggaggac	aagaagcaug	aacggcaucc	uaucuuugga	360
aacaucgucg	acgaaguggc	guaccacgaa	aaguacccga	ccaucuacca	ucugcggaag	420
aaguugguug	acucaacuga	caaggccgac	cucagauuga	ucuacuuggc	ccucgccc au	480
augaucaau	uccgcggaca	cuuccugauc	gaaggcgau	ugaaccug	uaacuccgac	540
guggauaagc	uuuucuuca	acuggugcag	accuacaacc	aacuguucga	agaaaaccca	600
aucaaugcua	gcggcgucga	ugccaaggcc	auccuguccg	cccggcuguc	gaagucgcgg	660
cgccucgaaa	accugaucgc	acagcugccg	ggagagaaaa	agaacggacu	uuucggcaac	720
uugaucgcuc	ucucacuggg	acucacuccc	aauuucaagu	ccaauuuuga	ccuggccgag	780
gacgcgaagc	ugcaacucuc	aaaggacacc	uacgacgacg	acuuggacaa	uuugcuggca	840
caaaauggcg	aucaguacgc	ggaucuguuc	cuugccgcua	agaaccuuuc	ggacgcaauc	900
uugcuguccg	auauccugcg	cgugaacacc	gaaauaacca	aagcgccgcu	uagcgccucg	960
augauuaagc	gguacgacga	gcaucaccag	gaucucacgc	ugcucaaagc	gcucgugaga	1020
cagcaacugc	cugaaaagua	caaggagauc	uucuucgacc	aguccaagaa	uggguacgca	1080
ggguacaucg	auggaggcgc	uagccaggaa	gaguucuaua	aguucaucaa	gccaauccug	1140
gaaaagaugg	acggaaccga	agaacugcug	gucaagcuga	acagggagga	ucugcuccgg	1200
aaacagagaa	ccuuugacaa	cggauccauu	ccccaccaga	uccaucuggg	ugagcugcac	1260
gccaucuugc	ggcgccagga	ggacuuuuac	ccauuccuca	aggacaaccg	ggaaaagauc	1320
gagaaaauuc	ugacguuccg	caucccgauu	uacgugggcc	cacuggcgcg	cggcaauucg	1380
cgcuucgcgu	ggaugacuag	aaaaucagag	gaaaccauca	cuccuuggaa	uuucgaggaa	1440
guuguggaua	agggagcuuc	ggcaciaaagc	uucaucgaac	gaaugaccaa	cuucgacaag	1500
aaucucccaa	acgagaaggu	gcuuccuaag	cacagccucc	uuuacgaaua	cuucacuguc	1560
uacaacgaac	ugacuaaagu	gaaaauacguu	acugaaggaa	ugaggaagcc	ggccuuucug	1620

uccggagaac	agaagaaagc	aaugugcga	cugcuguuca	agaccaaccg	caaggugacc	1680
gucaagcagc	uuaaagagga	cuacuuaag	aagaucgagu	guuucgacuc	aguggaaauc	1740
agcggggugg	aggacagauu	caacgcuucg	cugggaaccu	aucaugaucu	ccugaagauc	1800
aucaaggaca	aggacuuccu	ugacaacgag	gagaacgagg	acauccugga	agauaucguc	1860
cugaccuuga	ccuuuuucga	ggaucgag	augaucgagg	agaggcuuaa	gaccuacgcu	1920
caucucuucg	acgauaaggu	caugaaacaa	cucaagcgcc	gccgguacac	ugguuggggc	1980
cgccucuccc	gcaagcugau	caacgguaau	cgcgauaaac	agagcgguua	aacuauccug	2040
gauuuuccuca	aaucggau	cuucgcuaau	cguaacuuca	ugcaauugau	ccacgacgac	2100
agccugaccu	uuaaaggagga	cauccaaaaa	gcacaagugu	ccggacaggg	agacucacuc	2160
caugaacaca	ucgcgaau	ggccggau	ccggcgauua	agaagggaau	ucugcaaacu	2220
gugaaggugg	ucgacgagcu	ggugaagguc	augggacggc	acaaaccgga	gaauaucgug	2280
auugaaaugg	cccagaaaaa	ccagacuacc	cagaagggcc	agaaaaacuc	ccgcgaaagg	2340
augaagcggga	ucgaagaagg	aaucaaggag	cugggcagcc	agauccugaa	agagcacccg	2400
guggaaaaca	cgagcugca	gaacgagaag	cucuaccugu	acuauuugca	aaauggacgg	2460
gacauguacg	uggaccaaga	gcuggacauc	aaucgguugu	cugauuacga	cguggaccac	2520
aucguuccac	aguccuuucu	gaaggau	ucgaucgaua	acaagguguu	gacucgcagc	2580
gacaagaaca	gagggaaguc	agauaaugug	ccaucggagg	aggucgugaa	gaagaugaag	2640
aauuacuggc	ggcagcuccu	gaaugcgaag	cugauuaccc	agagaaaguu	ugacaauuc	2700
acuaaaagccg	agcgcggcgg	acucucagag	cuggauaagg	cuggauucau	caaacggcag	2760
cuggucgaga	cucggcagau	uaccaagcac	guggcgagca	ucuuggacuc	ccgcaugaac	2820
acuaaaauacg	acgagaacga	uaagcucauc	cggaaguga	aggugauuac	ccugaaaagc	2880
aaacuugugu	cggacuucg	gaaggacuuu	caguuuuaca	aagugagaga	aaucaacaac	2940
uaccaucacg	cgcaugacgc	auaccucaac	gcuguggucg	guaccgccc	gaucaaaaag	3000
uaccuuaaac	uugaau	guuuguguac	ggagacuaca	aggucuacga	cgugaggaag	3060
augauagcca	aguccgaaca	ggaaucggg	aaagcaacug	cgaaauacuu	cuuuuacuca	3120
aacaucauga	acuuuuucaa	gacugaaaau	acgcuggcca	auggagaaau	caggaagagg	3180
ccacugaucg	aaacuaacgg	agaaacgggc	gaaucgugu	gggacaaggg	cagggacuuc	3240

gcaacuguuc gcaaagugcu cucuaugccg caagucaaua uugugaagaa aaccgaagug	3300
caaaccggcg gauuuucaaa ggaaucgauc cucccaaaga gaaauagcga caagcucauu	3360
gcacgcaaga aagacuggga cccgaagaag uacggaggau ucgauucgcc gacugucgca	3420
uacuccgucc ucgugguggc caagguggag aagggaaaga gcaaaaagcu caaauccguc	3480
aaagagcugc uggggauuac caucauggaa cgauccucgu ucgagaagaa cccgauugau	3540
uuccucgagg cgaaggguaa caaggaggug aagaaggau ucgaucauaa acuccccaag	3600
uacucacugu ucgaacugga aaauggugcg aagcgcaugc ugguucggc cggagaacuc	3660
caaaaaggaa augagcuggc cuugccuagc aaguacguca acuuccucua ucuugcuucg	3720
cacuacgaaa aacucaaaagg gucaccggaa gauaacgaac agaagcagcu uuucguggag	3780
cagcacaagc auuauugga ugaaaucauc gaacaaauu ccgaguuuuc aaagcgcgug	3840
auccucgccg acgccaaccu cgacaaaguc cugucggccu acaauaagca uagagauaag	3900
ccgaucagag aacaggccga gaacauuau cacuuguuca ccugacuaa ccugggagcc	3960
ccagccgccu ucaaguacuu cgauacuacu aucgaucgca aaagauacac guccaccaag	4020
gaaguucugg acgcgacccu gauccaccaa 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
 865 870 875 880

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

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

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 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
 aaucugucg 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
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augaucaaga	gauacgacga	acaccaccag	gaccugacac	ugcugaaggc	acuggucaga	1020
cagcagcugc	cggaaaagua	caaggaaauc	uucuucgacc	agagcaagaa	cggauacgca	1080
ggauacaucg	acggaggagc	aagccaggaa	gaauucuaca	aguucaucaa	gccgauccug	1140
gaaaagaugg	acggaacaga	agaacugcug	gucaagcuga	acagagaaga	ccugcugaga	1200
aagcagagaa	cauucgacaa	cggaaagcauc	ccgcaccaga	uccaccuggg	agaacugcac	1260
gcaauccuga	gaagacagga	agacuucuac	ccguuccuga	aggacaacag	agaaaagauc	1320
gaaaagaucc	ugacauucag	aaucccgua	uacgucggac	cgcuaggcaag	aggaaacagc	1380
agauucgcau	ggaugacaag	aaagagcgaa	gaaacaauca	caccguggaa	cuucgaagaa	1440
gucgucgaca	aggagagcaag	cgcacagagc	uucaucgaaa	gaaugacaaa	cuucgacaag	1500
aaccugccga	acgaaaaggu	ccugccgaag	cacagccugc	uguacgaaua	cuucacaguc	1560
uacaacgaac	ugacaaaggu	caaguacguc	acagaaggaa	ugagaaaagcc	ggcauuccug	1620
agcggagaac	agaagaaggc	aaucgucgac	cugcuguuca	agacaaacag	aaaggucaca	1680
gucaagcagc	ugaaggaaga	cuacuucaag	aagaucgaau	gcuucgacag	cgucgaaauc	1740
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aucaaggaca	aggacuuccu	ggacaacgaa	gaaaacgaag	acauccugga	agacaucguc	1860
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caccuguucg	acgacaaggu	caugaagcag	cugaagagaa	gaagauacac	aggaugggga	1980
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agccugacau	ucaaggaaga	cauccagaag	gcacagguca	gcggacaggg	agacagccug	2160
cacgaacaca	ucgcaaaccu	ggcaggaagc	ccggcaauca	agaagggaau	ccugcagaca	2220
gucaaggucg	ucgacgaacu	ggucaagguc	augggaagac	acaagccgga	aaacaucguc	2280
aucgaaaugg	caagagaaaa	ccagacaaca	cagaaggggac	agaagaacag	cagagaaaaga	2340
augaagagaa	ucgaagaagg	aaucaaggaa	cugggaagcc	agauccugaa	ggaacacccg	2400
gucgaaaaca	cacagcugca	gaacgaaaag	cuguaccugu	acuaccugca	gaacggaaga	2460

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aucgucccg	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	cacaaagcac	gucgcacaga	uccuggacag	cagaaugaac	2820
acaaaguacg	acgaaaacga	caagcugauc	agagaaguca	aggucaucac	acugaagagc	2880
aagcugguca	gcgacuucag	aaaggacuuc	caguucuaca	aggucagaga	aaucaacaac	2940
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uacccgaagc	uggaaagcga	auucgucuac	ggagacuaca	aggucuacga	cgucagaaag	3060
augaucgcaa	agagcgaaca	ggaaaucgga	aaggcaacag	caaaguacuu	cuucuacagc	3120
aacaucauga	acuucuucua	gacagaaauc	acacuggcaa	acggagaaau	cagaaagaga	3180
ccgcugaucg	aaacaaacgg	agaaacagga	gaaaucgucu	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	aagggaaga	gcaagaagcu	gaagagcguc	3480
aaggaacugc	ugggaaucac	aaucauggaa	agaagcagcu	ucgaaaagaa	cccgaucgac	3540
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uacagccugu	ucgaacugga	aaacggaaga	aagagaaugc	uggcaagcgc	aggagaacug	3660
cagaagggaa	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	aacaagaauc	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
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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 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)

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cugcugagcg	acauccugag	agucaacaca	gaaauacaaa	aggcaccgcu	gagcgcaagc	960
augaucaaga	gauacgacga	acaccaccag	gaccugacac	ugcugaaggc	acuggucaga	1020
cagcagcugc	cggaaaagua	caaggaaauc	uucuucgacc	agagcaagaa	cggauacgca	1080
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agcggagaa	agaagaaggc	aaucgucgac	cugcuguuca	agacaaacag	aaaggucaca	1680
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agacugagca	gaaagcugau	caacggaauc	agagacaagc	agagcggaaa	gacaauccug	2040
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gucaaggucg	ucgacgaacu	ggucaagguc	augggaagac	acaagccgga	aaacaucguc	2280
aucgaaaugg	caagagaaaa	ccagacaaca	cagaaggggac	agaagaacag	cagagaaaaga	2340
augaagagaa	ucgaagaagg	aaucaaggaa	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	gaggaaagag	cgacaacguc	ccgagcgaag	aagucgucaa	gaagaugaag	2640
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cuggucgaaa	caagacagau	cacaaagcac	gucgcacaga	uccuggacag	cagaaugaac	2820
acaaaguacg	acgaaaacga	caagcugauc	agagaaguca	aggucaucac	acugaagagc	2880
aagcugguca	gcgacuucag	aaaggacuuc	caguucuaca	aggucagaga	aaucaacaac	2940
uaccaccacg	cacacgacgc	auaccugaac	gcagucgucg	gaacagcacu	gaucaagaag	3000
uacccgaagc	uggaaagcga	auucgucuac	ggagacuaca	aggucucaga	cgucagaaaag	3060
augaucgcaa	agagcgaaca	ggaaaucgga	aaggcaacag	caaaguacuu	cuucuacagc	3120
aacaucauga	acuucuuaa	gacagaaauc	acacuggcaa	acggagaaaau	cagaaagaga	3180
ccgcugaucg	aaacaaacgg	agaaacagga	gaaaucgucu	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	uggucgucgc	aaaggucgaa	aagggaaaga	gcaagaagcu	gaagagcguc	3480
aaggaacugc	ugggaaucaac	aaucauggaa	agaagcagcu	ucgaaaagaa	cccgaucgac	3540
uuccuggaag	caaagggaua	caaggaaguc	aagaaggacc	ugaucauca	gcugccgaag	3600
uacagccugu	ucgaacugga	aaacggaaga	aagagaauGC	uggcaagcgc	aggagaacug	3660
cagaagggaa	acgaacuggc	acugccgagc	aaguacguca	acuuccugua	ccuggcaagc	3720
cacuacgaaa	agcugaaggg	aagcccggaa	gacaacgaac	agaagcagcu	guucgucgaa	3780
cagcacaagc	acuaccugga	cgaaaaucauc	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	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
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 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	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	acaaggucau	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	aggaagcccc	gcaaucaaga	agggaauccu	gcagacaguc	2220
aaggucgucg	acgaacuggu	caaggucaug	ggaagacaca	agccggaaaa	caucgucauc	2280
gaaauggcaa	gagaaaacca	gacaacacag	aagggaacaga	agaacagcag	agaaagaau	2340
aagagaauucg	aagaaggaau	caaggaacug	ggaagccaga	uccugaagga	acacccgguc	2400
gaaaacacac	agcugcagaa	cgaaaagcug	uaccuguacu	accugcagaa	cggaagagac	2460
auguacgucg	accaggaacu	ggacaucaac	agacugagcg	acuacgacgu	cgaccacauc	2520
gucccgagaga	gcuuccugaa	ggacgacagc	aucgacaaca	agguccugac	aagaagcgac	2580
aagaacagag	gaaagagcga	caacgucccc	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	ucagagaaa	caacaacuac	2940
caccacgcac	acgacgcaua	ccugaacgca	gucgucggaa	cagcacugau	caagaaguac	3000
ccgaagcugg	aaagcgaaau	cgucuacgga	gacuacaagg	ucuacgacgu	cagaaagaug	3060
aucgcaaaga	gcgaacagga	aaucggaaag	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	acagcccgac	agucgcgauac	3420
agcguccugg	ucgucgcaaa	ggucgaaaag	ggaaagagca	agaagcugaa	gagcgucaag	3480
gaacugcugg	gaucacaa	cauggaaaga	agcagcuucg	aaaagaaccc	gaucgacuuc	3540
cuggaagcaa	agggauacaa	ggaagucaag	aaggaccuga	ucaucaagcu	gccgaaguac	3600
agccuguucg	aacuggaaaa	cggaagaaa	agaugcugg	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 cacaaaggaa	4020
guccuggacg caacacugau ccaccagagc aucacaggac uguacgaaac aagaaucgac	4080
cugagccagc ugggaggaga cggaggagga agcccgaaga agaagagaaa gguc	4134

<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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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 acccgacaa 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	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	cguggaacu	cgaagaaguc	1440
gucgacaagg	gagcaagcgc	acagagcuuc	aucgaaagaa	ugacaaacu	cgacaagaac	1500
cugccgaacg	aaaagguccu	gccgaagcac	agccugcugu	acgaauacu	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	acaaggucau	gaagcagcug	aagagaagaa	gauacacagg	auggggaaga	1980
cugagcagaa	agcugaucaa	cggaaucaga	gacaagcaga	gcggaaagac	aauccuggac	2040
uuccugaaga	gcgacggauu	cgcaaacaga	aacuucaugc	agcugaucca	cgacgacagc	2100
cugacauuca	aggaagacau	ccagaaggca	caggucagcg	gacagggaga	cagccugcac	2160
gaacacaucg	caaaccuggc	aggaagcccc	gcaaucaaga	agggaauccu	gcagacaguc	2220
aaggucgucg	acgaacuggu	caaggucaug	ggaagacaca	agccggaaaa	caucgucauc	2280
gaaauggcaa	gagaaaacca	gacaacacag	aaggggacaga	agaacagcag	agaaagaau	2340
aagagaau	cg	g	g	g	g	2400
gaaaacacac	agcugcagaa	cgaaaagcug	uaccuguacu	accugcagaa	cggaagagac	2460

auguacgucg	accaggaacu	ggacaucaac	agacugagcg	acuacgacgu	cgaccacauc	2520
gucccgagag	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	ucagagaaa	caacaacuac	2940
caccacgcac	acgacgcaua	ccugaacgca	gucgucggaa	cagcacugau	caagaaguac	3000
ccgaagcugg	aaagcgaauu	cgucuacgga	gacuacaagg	ucuacgacgu	cagaaagaug	3060
aucgcaaaga	gcgaacagga	aaucggaaag	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	acagcccgac	agucgcgauac	3420
agcguccugg	ucgucgcaaa	ggucgaaaag	ggaaagagca	agaagcugaa	gagcgucaag	3480
gaacugcugg	gaaucacaau	cauggaaaga	agcagcuucg	aaaagaaccc	gaucgacuuc	3540
cuggaagcaa	agggauacaa	ggaagucaag	aaggaccuga	ucaucaagcu	gccgaaguac	3600
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aagggaacg	aacuggcacu	gccgagcaag	uacgucaacu	uccuguaccu	ggcaagccac	3720
uacgaaaagc	ugaagggaag	cccggaagac	aacgaacaga	agcagcuguu	cgucgaacag	3780
cacaagcacu	accuggacga	aaucaucgaa	cagaucagcg	aauucagcaa	gagagucauc	3840
cuggcagacg	caaaccugga	caagguccug	agcgcauaca	acaagcacag	agacaagccg	3900
aucagagaac	aggcagaaaa	caucauccac	cuguucacac	ugacaaaaccu	gggagcaccg	3960
gcagcauuca	aguacuucga	cacaacaau	gacagaaaga	gauacacaag	cacaaaggaa	4020
guccuggacg	caacacugau	ccaccagagc	aucacaggac	uguacgaaac	aagaaucgac	4080

cugagccagc ugggaggaga cggaggagga agcccgaaga agaagagaaa gguc 4134

<210> 212

<211> 4134

<212> ARN

<213> Secuencia artificial

<220>

<223> Sintético: secuencia de codificación desnuda de dCas9

<400> 212

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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 gagaaagaag 420

cuggucgaca gcacagacaa ggcagaccug agacugaucu accuggcacu ggcacacaug 480

aucaaguuca gaggacacuu ccugaucgaa ggagaccuga acccgacaa cagcgacguc 540

gacaagcugu ucauccagcu gguccagaca uacaaccagc uguucgaaga aaacccgauc 600

aacgcaagcg gagucgacgc aaaggcaauc cugagcgcaa gacugagcaa gaggagaaga 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

uacaucgacg gaggagcaag ccaggaagaa uucaacaagu ucaucaagcc gaucgaggaa 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	acaaggucau	gaagcagcug	aagagaagaa	gauacacagg	auggggaaga	1980
cugagcagaa	agcugaucaa	cggaaucaga	gacaagcaga	gcggaagac	aauccuggac	2040
uuccugaaga	gcgacggauu	cgcaaacaga	aacucaugc	agcugaucca	cgacgacagc	2100
cugacauuca	aggaagacau	ccagaaggca	caggucagcg	gacagggaga	cagccugcac	2160
gaacacaucg	caaaccuggc	aggaagccccg	gcaaucaaga	agggaauccu	gcagacaguc	2220
aaggucgucg	acgaacuggu	caaggucaug	ggaagacaca	agccggaaaa	caucgucauc	2280
gaaauggcaa	gagaaaacca	gacaacacag	aagggaacaga	agaacagcag	agaaagaaug	2340
aagagaauucg	aagaaggaau	caaggaacug	ggaagccaga	uccugaagga	acacccgguc	2400
gaaaacacac	agcugcagaa	cgaaaagcug	uaccuguacu	accugcagaa	cggaagagac	2460
auguacgucg	accaggaacu	ggacaucaac	agacugagcg	acuacgacgu	cgacgcaauc	2520
gucccgacga	gcuuccugaa	ggacgacagc	aucgacaaca	agguccugac	aagaagcgac	2580
aagaacagag	gaaagagcga	caacguccccg	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	ucagagaaa	caacaacuac	2940
caccacgcac	acgacgcau	ccugaacgca	gucgucggaa	cagcacugau	caagaaguac	3000
ccgaagcugg	aaagcgaau	cgucuacgga	gacuacaagg	ucuacgacgu	cagaaaug	3060
aucgcaaaga	gcgaacagga	aaucggaaag	gcaacagcaa	aguacuucu	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	acagcccgac	agucgcgauac	3420
agcguccugg	ucgucgcaaa	ggucgaaaag	ggaaagagca	agaagcugaa	gagcguaag	3480
gaacugcugg	gaucacaa	cauggaaaga	agcagcuucg	aaaagaacc	gaucgacuuc	3540
cuggaagcaa	agggauacaa	ggaagucaag	aaggaccuga	ucaucaagcu	gccgaaguac	3600
agccuguucg	aacuggaaaa	cggagaaag	agaugcugg	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
gcagcauuc	aguacuucga	cacaacauc	gacagaaaga	gauacacaag	cacaaaggaa	4020
guccuggacg	caacacugau	ccaccagagc	aucacaggac	uguacgaaac	aagaaucgac	4080
cugagccagc	ugggaggaga	cggaggagga	agcccgaaga	agaagagaaa	gguc	4134

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

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

<400> 213

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
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
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 aaaucaaggu cccgagcaag aaguucaagg uccugggaaa cacagacaga 120

cacagcauca agaagaaccu gaucggagca cugcuguucg acagcggaga aacagcagaa 180

gcaacaagac ugaagagaac agcaagaaga agauacacaa gaagaaagaa cagaauucgc 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	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	aguucaucaa	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	cgucggcaag	aggaaacagc	1380
agauucgcau	ggaugacaag	aaagagcgaa	gaaacaauca	caccguggaa	cuucgaagaa	1440
gucgucgaca	aggagcaag	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	agaaacuuca	ugcagcugau	ccacgacgac	2100
agccugacau	ucaaggaaga	cauccagaag	gcacagguca	gcggacaggg	agacagccug	2160
cacgaacaca	ucgcaaaccu	ggcaggaagc	ccggcaauca	agaagggaau	ccugcagaca	2220

gucaaggucg	ucgacgaacu	ggucaagguc	augggaagac	acaagccgga	aaacaucguc	2280
aucgaaaugg	caagagaaaa	ccagacaaca	cagaagggac	agaagaacag	cagagaaaaga	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	gaggaaagag	cgacaacguc	ccgagcgaag	aagucgucaa	gaagaugaag	2640
aacuacugga	gacagcugcu	gaacgcaaag	cugaucacac	agagaaaguu	cgacaaccug	2700
acaaaggcag	agagaggagg	acugagcgaa	cuggacaagg	caggauucau	caagagacag	2760
cuggucgaaa	caagacagau	cacaaagcac	gucgcacaga	uccuggacag	cagaaugaac	2820
acaaaguacg	acgaaaacga	caagcugauc	agagaaguca	aggucaucac	acugaagagc	2880
aagcugguca	gcgacuucag	aaaggacuuc	caguucuaca	aggucagaga	aaucaacaac	2940
uaccaccacg	cacacgacgc	auaccugaac	gcagucgucg	gaacagcacu	gaucaagaag	3000
uacccgaagc	uggaaagcga	auucgucuac	ggagacuaca	aggucuacga	cgucagaaag	3060
augaucgcaa	agagcgaaca	ggaaaucgga	aaggcaacag	caaaguacuu	cuucuacagc	3120
aacaucauga	acuucuucua	gacagaaauc	acacuggcaa	acggagaaaau	cagaaagaga	3180
ccgcugaucg	aaacaaacgg	agaaacagga	gaaaucgucu	gggacaaggg	aagagacuuc	3240
gcaacaguca	gaaaggguccu	gagcaugccg	caggucaaca	ucgucaagaa	gacagaaguc	3300
cagacaggag	gauucagcaa	ggaaagcauc	cugccgaaga	gaaacagcga	caagcugauc	3360
gcaagaaaga	aggacuggga	cccgaagaag	uacggaggau	ucgacagccc	gacagucgca	3420
uacagcgucc	uggucgucgc	aaaggucgaa	aagggaaga	gcaagaagcu	gaagagcguc	3480
aaggaacugc	ugggaauac	aaucauggaa	agaagcagcu	ucgaaaagaa	cccgaucgac	3540
uuccuggaag	caaagggaau	caaggaaguc	aagaaggacc	ugaucauca	gcugccgaag	3600
uacagccugu	ucgaacugga	aaacggaaga	aagagaau	uggcaagcgc	aggagaacug	3660
cagaagggaa	acgaacuggc	acugccgagc	aaguacguca	acuuccugua	ccuggcaagc	3720
cacuacgaaa	agcugaaggg	aagcccggaa	gacaacgaac	agaagcagcu	guucgucgaa	3780
cagcacaagc	acuaccugga	cgaaaaucauc	gaacagauca	gcgaauucag	caagagaguc	3840

auccuggcag acgcaaaccu ggacaagguc cugagcgcau acaacaagca cagagacaag	3900
ccgaucagag aacaggcaga aaacaucauc caccuguuca cacugacaaa ccuggggagca	3960
ccggcagcau ucaaguacuu cgacacaaca aucgacagaa agagauacac aagcacaag	4020
gaaguccugg acgcaacacu gauccaccag agcaucacag gacuguacga aacaagauc	4080
gaccugagcc agcuggggagg 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 acuggacau ggaacaaaca gcgucggaug ggcagucauc	60
acagacgaau acaaggucc 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 acccgacaa 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	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	cguggaacu	cgaagaaguc	1440
gucgacaagg	gagcaagcgc	acagagcuuc	aucgaaagaa	ugacaaacu	cgacaagaac	1500
cugccgaacg	aaaagguccu	gccgaagcac	agccugcugu	acgaauacu	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	acaaggucau	gaagcagcug	aagagaagaa	gauacacagg	auggggaaga	1980
cugagcagaa	agcugaucaa	cggaaucaga	gacaagcaga	gcggaagac	aauccuggac	2040
uuccugaaga	gcgacggauu	cgcaaacaga	aacucaugc	agcugaucca	cgacgacagc	2100
cugacauuca	aggaagacau	ccagaaggca	caggucagcg	gacagggaga	cagccugcac	2160
gaacacaucg	caaaccuggc	aggaagcccc	gcaaucaaga	agggaauccu	gcagacaguc	2220
aaggucgucg	acgaacuggu	caaggucaug	ggaagacaca	agccggaaaa	caucgucauc	2280
gaaauggcaa	gagaaaacca	gacaacacag	aagggacaga	agaacagcag	agaaagaau	2340
aagagaaucg	aagaaggaau	caaggaacug	ggaagccaga	uccugaagga	acacccgguc	2400
gaaaacacac	agcugcagaa	cgaaaagcug	uaccuguacu	accugcagaa	cggaagagac	2460
auguacgucg	accaggaacu	ggacaucaac	agacugagcg	acuacgacgu	cgaccacauc	2520

gucccgagag	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	ucagagaaa	caacaacuac	2940
caccacgcac	acgacgcaua	ccugaacgca	gucgucggaa	cagcacugau	caagaaguac	3000
ccgaagcugg	aaagcgaaau	cgucuacgga	gacuacaagg	ucuacgacgu	cagaaagaug	3060
aucgcaaaga	gcgaacagga	aaucggaaag	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	acagcccgac	agucgcgauac	3420
agcguccugg	ucgucgcaaa	ggucgaaaag	ggaaagagca	agaagcugaa	gagcgucaag	3480
gaacugcugg	gaucacaau	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	ugacaaaaccu	gggagcaccg	3960
gcagcauuc	aguacuucga	cacaacaau	gacagaaaga	gauacacaag	cacaaaggaa	4020
guccuggacg	caacacugau	ccaccagagc	aucacaggac	uguacgaaac	aagaaucgac	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 1250	Gln Leu Phe Val 1255	Glu Gln His Lys 1260
His Tyr Leu Asp Glu Ile 1265	Ile Glu Gln Ile Ser 1270	Glu Phe Ser Lys 1275
Arg Val Ile Leu Ala Asp 1280	Ala Asn Leu Asp Lys 1285	Val Leu Ser Ala 1290
Tyr Asn Lys His Arg Asp 1295	Lys Pro Ile Arg Glu 1300	Gln Ala Glu Asn 1305
Ile Ile His Leu Phe Thr 1310	Leu Thr Asn Leu Gly 1315	Ala Pro Ala Ala 1320
Phe Lys Tyr Phe Asp Thr 1325	Thr Ile Asp Arg Lys 1330	Arg Tyr Thr Ser 1335
Thr Lys Glu Val Leu Asp 1340	Ala Thr Leu Ile His 1345	Gln Ser Ile Thr 1350
Gly Leu Tyr Glu Thr Arg 1355	Ile Asp Leu Ser Gln 1360	Leu Gly Gly Asp 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 aaucacaggu cccgagcaag aaguucaagg uccugggaaa cacagacaga 120
 cacagcauca agaagaaccu gaucggagca cugcuguucg acagcggaga aacagcagaa 180

gcaacaagac ugaagagaac agcaagaaga agauacacaa gaagaaagaa cagaauucgc	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 cgacgcaauc	900
cugcugagcg acauccugag agucaacaca gaaucacaa aggcaccgcu gagcgcaagc	960
augaucaaga gauacgacga acaccaccag gaccugacac ugcugaaggc acuggucaga	1020
cagcagcugc cggaagagua caaggaauc uucuucgacc agagcaagaa cggauacgca	1080
ggauacaucg acggaggagc aagccaggaa gaauucuaca aguucauca gccgauccug	1140
gaaaagaugg acggaacaga agaacugcug gucaagcuga acagagaaga ccugcugaga	1200
aagcagagaa cauucgaca cggaagcauc ccgcaccaga uccaccuggg agaacugcac	1260
gcaauccuga gaagacagga agacuucuac ccguuccuga aggacaacag agaaaagauc	1320
gaaaagaucc ugacauucag aaucccgua uacgucggac cgcuggcaag aggaaacagc	1380
agauucgcau ggaugacaag aaagagcgaa gaaacaauca caccguggaa 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 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	agaaacuuca	ugcagcugau	ccacgacgac	2100
agccugacau	ucaaggaaga	cauccagaag	gcacagguca	gcggaacagg	agacagccug	2160
cacgaacaca	ucgcaaaccu	ggcaggaagc	ccggcaauca	agaagggaau	ccugcagaca	2220
gucaaggucg	ucgacgaacu	ggucaagguc	augggaagac	acaagccgga	aaacaucguc	2280
aucgaaaugg	caagagaaaa	ccagacaaca	cagaagggac	agaagaacag	cagagaaaaga	2340
augaagagaa	ucgaagaagg	aaucaaggaa	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	cacaaagcac	gucgcacaga	uccuggacag	cagaaugaac	2820
acaaaguacg	acgaaaacga	caagcugauc	agagaaguca	aggucaucac	acugaagagc	2880
aagcugguca	gcgacuucag	aaaggacuuc	caguucuaca	aggucagaga	aaucaacaac	2940
uaccaccacg	cacacgacgc	auaccugaac	gcagucgucg	gaacagcacu	gaucaagaag	3000
uacccgaagc	uggaaagcga	auucgucuac	ggagacuaca	aggucuacga	cgucagaaaag	3060
augaucgcaa	agagcgaaca	ggaaaucgga	aaggcaacag	caaaguacuu	cuucuacagc	3120
aacaucauga	acuucuucua	gacagaaauc	acacuggcaa	acggagaaaau	cagaaagaga	3180
ccgcugaucg	aaacaaacgg	agaaacagga	gaaaucgucu	gggacaaggg	aagagacuuc	3240
gcaacaguca	gaaagguccu	gagcaugccg	caggucaaca	ucgucaagaa	gacagaaguc	3300
cagacaggag	gauucagcaa	ggaaagcauc	cugccgaaga	gaaacagcga	caagcugauc	3360
gcaagaaaaga	aggacuggga	cccgaagaag	uacggaggau	ucgacagccc	gacagucgca	3420

uacagcgucc	uggucgucgc	aaaggucgaa	aagggaaaga	gcaagaagcu	gaagagcguc	3480
aaggaacugc	ugggaaucac	aaucauggaa	agaagcagcu	ucgaaaagaa	cccgau cgac	3540
uuccuggaag	caaagggaua	caaggaaguc	aagaaggacc	ugaucauca	gcugccgaag	3600
uacagccugu	ucgaacugga	aaacggaaga	aagagaau gc	uggcaagcgc	aggagaacug	3660
cagaagggaa	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	aacaagaau c	4080
gaccugagcc	agcuggggagg	agacuag				4107

<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	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	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	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	acaaggucau	gaagcagcug	aagagaagaa	gauacacagg	auggggaaga	1980
cugagcagaa	agcugaucaa	cggaaucaga	gacaagcaga	gcggaaagac	aauccuggac	2040
uuccugaaga	gcgacggauu	cgcaaacaga	aacuucaugc	agcugaucca	cgacgacagc	2100

cugacauuca	aggaagacau	ccagaaggca	caggucagcg	gacagggaga	cagccugcac	2160
gaacacaucg	caaaccuggc	aggaagcccc	gcaaucaaga	agggaauccu	gcagacaguc	2220
aaggucgucg	acgaacuggu	caaggucaug	ggaagacaca	agccggaaaa	caucgucauc	2280
gaaauggcaa	gagaaaacca	gacaacacag	aaggacagag	agaacagcag	agaaagaug	2340
aagagaaucg	aagaaggaau	caaggaacug	ggaagccaga	uccugaagga	acacccgguc	2400
gaaaacacac	agcugcagaa	cgaaaagcug	uaccuguacu	accugcagaa	cggaagagac	2460
auguacgucg	accaggaacu	ggacaucaac	agacugagcg	acuacgacgu	cgaccacauc	2520
gucccgagag	gcuuccugaa	ggacgacagc	aucgacaaca	agguccugac	aagaagcgac	2580
aagaacagag	gaaagagcga	caacgucccc	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	ucagagaaa	caacaacuac	2940
caccacgcac	acgacgcaua	ccugaacgca	gucgucggaa	cagcacugau	caagaaguac	3000
ccgaagcugg	aaagcgaaau	cgucuacgga	gacuacaagg	ucuacgacgu	cagaaagaug	3060
aucgcaaaga	gcgaacagga	aaucggaaag	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	acagcccgac	agucgcgauac	3420
agcguccugg	ucgucgcaaa	ggucgaaaag	ggaaagagca	agaagcugaa	gagcgucaag	3480
gaacugcugg	gaucacaa	cauggaaaga	agcagcuucg	aaaagaaccc	gaucgacuuc	3540
cuggaagcaa	agggauacaa	ggaagucaag	aaggaccuga	ucaucaagcu	gccgaaguac	3600
agccuguucg	aacuggaaaa	cggaagaaaag	agaugcugg	caagcgagcag	agaacugcag	3660
aagggaacg	aacuggcacu	gccgagcaag	uacgucaacu	uccuguaccu	ggcaagccac	3720

uacgaaaagc ugaagggaag cccggaagac aacgaacaga agcagcuguu cgucgaacag 3780
 cacaagcacu accugggacga aaucaucgaa cagaucagcg aaucagcaa gagagucauc 3840
 cuggcagacg caaaccugga caagguccug agcgcauaca acaagcacag agacaagccg 3900
 aucagagaac aggcagaaaa caucauccac cuguucacac ugacaaaccu gggagcaccg 3960
 gcagcauucagu aguacuucga cacaacauc gacagaaaga gauacacaag cacaaaggaa 4020
 guccuggacg caacacugau ccaccagagc aucacaggac uguacgaaac aagaaucgac 4080
 cugagccagc ugggaggaga 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 aaauucuag 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 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 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 aaucccguac uacgucggac cgcuggcaag aggaaacagc	1380

agauucgcau	ggaugacaag	aaagagcgaa	gaaacaauca	caccguggaa	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	aggauggggga	1980
agacugagca	gaaagcugau	caacggaauc	agagacaagc	agagcggaaa	gacaauccug	2040
gacuuccuga	agagcgacgg	auucgcaaac	agaaacuuca	ugcagcugau	ccacgacgac	2100
agccugacau	ucaaggaaga	cauccagaag	gcacagguca	gcggaacagg	agacagccug	2160
cacgaacaca	ucgcaaaccu	ggcaggaagc	ccggcaauca	agaagggaau	ccugcagaca	2220
gucaaggucg	ucgacgaacu	ggucaagguc	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	cgucgacgca	2520
aucgucccg	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	cacaaagcac	gucgcacaga	uccuggacag	cagaaugaac	2820
acaaaguacg	acgaaaacga	caagcugauc	agagaaguca	aggucaucac	acugaagagc	2880
aagcugguca	gcgacuucag	aaaggacuuc	caguucuaca	agguacagaga	aaucaacaac	2940
uaccaccacg	cacacgacgc	auaccugaac	gcagucgucg	gaacagcacu	gaucaagaag	3000

uacccgaagc	uggaaagcga	auucgucuac	ggagacuaca	aggucuacga	cgucagaaag	3060
augaucgcaa	agagcgaaca	ggaaaucgga	aaggcaacag	caaaguacuu	cuucuacagc	3120
aacaucauga	acuucuuaa	gacagaaauc	acacuggcaa	acggagaaaau	cagaaagaga	3180
ccgcugaucg	aaacaaacgg	agaaacagga	gaaaucgucu	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	uggucgucgc	aaaggucgaa	aagggaaaga	gcaagaagcu	gaagagcguc	3480
aaggaacugc	ugggaauac	aaucauggaa	agaagcagcu	ucgaaaagaa	cccgau cgac	3540
uuccuggaag	caaagggaua	caaggaaguc	aagaaggacc	ugaucaucaa	gcugccgaag	3600
uacagccugu	ucgaacugga	aaacggaaga	aagagaau gc	uggcaagcgc	aggagaacug	3660
cagaagggaa	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	aagcaciaaag	4020
gaaguccugg	acgcaacacu	gauccaccag	agcaucacag	gacuguacga	aacaagaau c	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 N0: 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	gcgagagaaac	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	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	cgcaaucug	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	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	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	acaaggucan	gaagcagcug	aagagaagaa	gauacacagg	auggggaaga	1980
cugagcagaa	agcugaucaa	cggaaucaga	gacaagcaga	gcggaagac	aauccuggac	2040
uuccugaaga	gcgacggauu	cgcaaacaga	aacucaugc	agcugaucca	cgacgacagc	2100
cugacauuca	aggaagacau	ccagaaggca	caggucagcg	gacagggaga	cagccugcac	2160
gaacacaucg	caaaccuggc	aggaagcccg	gcaaucaaga	agggaauccu	gcagacaguc	2220
aaggucgucg	acgaacuggu	caaggucaug	ggaagacaca	agccggaaaa	caucgucauc	2280
gaaauggcaa	gagaaaacca	gacaacacag	aaggacagaa	agaacagcag	agaaagaau	2340
aagagaau	caaggaacug	ggaagccaga	uccugaagga	acacccgguc		2400
gaaaacacac	agcugcagaa	cgaaaagcug	uaccuguacu	accugcagaa	cggaagagac	2460
auguacgucg	accaggaacu	ggacaucaac	agacugagcg	acuacgacgu	cgacgcauc	2520
gucccgagaa	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	ucagagaaa	caacaacuac	2940
caccacgcac	acgacgcaua	ccugaacgca	gucgucggaa	cagcacugau	caagaaguac	3000
ccgaagcugg	aaagcgaauu	cgucuacgga	gacuacaagg	ucuacgacgu	cagaaagaug	3060
aucgcaaaga	gcgaacagga	aaucggaaa	gcaacagcaa	aguacuucuu	cuacagcaac	3120
aucaugaacu	ucuucaagac	agaaaucaca	cuggcaaacg	gagaaucag	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 acagcccgac agucgcgauac 3420
 agcguccugg ucgucgcaaa ggucgaaaag ggaaagagca agaagcugaa gagcguaag 3480
 gaacugcugg gaaucacaau cauggaaaga agcagcuucg aaaagaaccc gaucgacuuc 3540
 cuggaagcaa agggauacaa ggaagucaag aaggaccuga ucaucaagcu gccgaaguac 3600
 agccuguucg aacugggaaaa cggaagaaag agaaucgugg 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
 gcagcauucg aguacuucga cacaacauc gacagaaaga gauacacaag cacaaaggaa 4020
 guccuggacg caacacugau ccaccagagc aucacaggac uguacgaaac aagaaucgac 4080
 cugagccagc ugggaggaga cggaggagga agc 4113

<210> 222
 <211> 1392
 <212> PRT
 <213> Secuencia artificial

<220>
 <223> Sintético: secuencia de aminoácidos de Cas9 con dos señales de localización nuclear (2xNLS) como los aminoácidos C-terminales

<400> 222

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
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 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
 aaucugucg acgaagucgc auaccacgaa aaguaccga 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	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	aguucaucaa	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	caccguggaa	cuucgaagaa	1440
gucgucgaca	aggagcaag	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	gcfgacaggg	agacagccug	2160
cacgaacaca	ucgcaaaccu	ggcaggaagc	ccggcaauca	agaagggaau	ccugcagaca	2220
gucaaggucg	ucgacgaacu	ggucaagguc	augggaagac	acaagccgga	aaacaucguc	2280
aucgaaaugg	caagagaaaa	ccagacaaca	cagaagggac	agaagaacag	cagagaaaaga	2340

augaagagaa ucgaagaagg aaUCAaggaa cugggaagcc agaUccugaa ggaacacccg	2400
gucgaaaaca cacagcugca gaacgaaaag cuguaccugu acuaccugca gaacggaaga	2460
gacauguacg ucgaccagga acuggacauc aacagacuga gcgacuacga cgucgaccac	2520
aucgucccgC agagcuuccu gaaggacgac agcaucgaca acaagguccu gacaagaagc	2580
gacaagaaca gaggaaagag cgacaacguc ccgagcgaag aagucgucaa gaagaugaag	2640
aacuacugga gacagcugcu gaacgcaaag cugaucacac agagaaaguu cgacaaccug	2700
acaaaggcag agagaggagg acugagcgaa cuggacaagg caggauuau caagagacag	2760
cuggucgaaa caagacagau cacaaagcac gucgcacaga uccuggacag cagaaugaac	2820
acaaaguacg acgaaaacga caagcugauc agagaaguca aggucaucac acugaagagc	2880
aagcugguca gcgacuucag aaaggacuuc caguucuaca agguCagaga aaUCAaCaac	2940
uaccaccacg cacacgacgc auaccugaac gcagucgucg gaacagcacu gaucaagaag	3000
uacccgaagc uggaaagcga auucgucuac ggagacuaca agguCuacga cgucagaaag	3060
augaucgcaa agagcgaaca ggaaucgga aaggcaacag caaaguacuu cuucuacagc	3120
aacauauga acuucuuaa gacagaauc 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 uggucgucgc aaaggucgaa aagggaaga gcaagaagcu gaagagcguc	3480
aaggaacugc ugggaucac aaUCAaggaa agaagcagcu ucgaaaagaa cccgaucgac	3540
uuccuggaag caaagggaUa caaggaaguc aagaaggacc ugaucauaa gcugccgaag	3600
uacagccugu ucgaacugga aaacggaaga aagagaagc uggcaagcgC 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 aagcacaaag	4020
gaaguccugg acgcaacacu gauccaccag agcaucacag gacuguacga aacaagaau	4080
gaccugagcc agcuggggagg agacggagga ggaagcccga agaagaagag aaagguc	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 acuggacau	60
ggaacaaaca gcgucggaug ggcagucau	
acagacgaau acaaggucc gagcaagaag uucaaggucc	120
ugggaaacac agacagacac	
agcaucaaga agaaccugau cggagcacug	180
cuguucgaca gcggagaaac agcagaagca	
acaagacuga agagaacagc aagaagaaga uacacaagaa	240
gaaagaacag aaucugcuac	
cugcaggaaa ucuucagcaa cgaaauggca	300
aaggucgacg acagcuucuu ccacagacug	
gaagaaagcu uccuggucga agaagacaag	360
aagcacgaaa gacacccgau cuucggaaac	
aucgucgacg aagucgcaua ccacgaaaag	420
uacccgacaa ucuaccaccu gagaaagaag	
cuggucgaca gcacagacaa ggcagaccug	480
agacugaucu accuggcacu ggcacacaug	
aucaaguuca gaggacacuu ccugaucgaa	540
ggagaccuga acccgacaa cagcgacguc	
gacaagcugu ucauccagcu gguccagaca	600
uacaaccagc uguucgaaga aaacccgauc	
aacgcaagcg gagucgacgc aaaggcaauc	660
cugagcgcaa gacugagcaa gagcagaaga	
cuggaaaacc ugaucgcaca gcugccggga	720
gaaaagaaga acggacuguu cggaaccug	
aucgcacuga gccugggacu gacaccgaac	780
uucaagagca acuucgaccu ggcagaagac	
gcaaagcugc agcugagcaa ggacacauac	840
gacgacgacc uggacaaccu gcuggcacag	
aucggagacc aguacgcaga ccuguuccug	900
gcagcaaaga accugagcga cgcaauccug	

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	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	acaaggucau	gaagcagcug	aagagaagaa	gauacacagg	auggggaaga	1980
cugagcagaa	agcugaucaa	cggaaucaga	gacaagcaga	gcggaagac	aauccuggac	2040
uuccugaaga	gcgacggauu	cgcaaacaga	aacucaugc	agcugaucca	cgacgacagc	2100
cugacauuca	aggaagacau	ccagaaggca	caggucagcg	gacagggaga	cagccugcac	2160
gaacacaucg	caaaccuggc	aggaagccccg	gcaaucaaga	agggaauccu	gcagacaguc	2220
aaggucgucg	acgaacuggu	caaggucaug	ggaagacaca	agccggaaaa	caucgucauc	2280
gaaauggcaa	gagaaaacca	gacaacacag	aagggacaga	agaacagcag	agaaagaau	2340
aagagaaucg	aagaaggaau	caaggaacug	ggaagccaga	uccugaagga	acacccgguc	2400
gaaaacacac	agcugcagaa	cgaaaagcug	uaccuguacu	accugcagaa	cggaagagac	2460
auguacgucg	accaggaacu	ggacaucaac	agacugagcg	acuacgacgu	cgaccacauc	2520

gucccgagag	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	ucagagaaa	caacaacuac	2940
caccacgcac	acgacgcaua	ccugaacgca	gucgucggaa	cagcacugau	caagaaguac	3000
ccgaagcugg	aaagcgaaau	cgucuacgga	gacuacaagg	ucuacgacgu	cagaaagaug	3060
aucgcaaaga	gcgaacagga	aaucggaaag	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	acagcccgac	agucgcgauac	3420
agcguccugg	ucgucgcaaa	ggucgaaaag	ggaaagagca	agaagcugaa	gagcgucaag	3480
gaacugcugg	gaucacaau	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	ugacaaaaccu	gggagcaccg	3960
gcagcauucg	aguacuucga	cacaacaau	gacagaaaga	gauacacaag	cacaaaggaa	4020
guccuggacg	caacacugau	ccaccagagc	aucacaggac	uguacgaaac	aagaaucgac	4080
cugagccagc	ugggaggaga	cggaggagga	agcccgaaga	agaagagaaa	ggucccggaag	4140

aagaagagaa aggcggaag 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 1025 1030	Lys Ala Thr Ala	Lys Tyr Phe Phe 1035
Tyr Ser Asn Ile Met Asn Phe 1040 1045	Phe Lys Thr Glu	Ile Thr Leu Ala 1050
Asn Gly Glu Ile Arg Lys Arg 1055 1060	Pro Leu Ile Glu	Thr Asn Gly Glu 1065
Thr Gly Glu Ile Val Trp Asp 1070 1075	Lys Gly Arg Asp	Phe Ala Thr Val 1080
Arg Lys Val Leu Ser Met Pro 1085 1090	Gln Val Asn Ile	Val Lys Lys Thr 1095
Glu Val Gln Thr Gly Gly Phe 1100 1105	Ser Lys Glu Ser	Ile Leu Pro Lys 1110
Arg Asn Ser Asp Lys Leu Ile 1115 1120	Ala Arg Lys Lys	Asp Trp Asp Pro 1125
Lys Lys Tyr Gly Gly Phe Asp 1130 1135	Ser Pro Thr Val	Ala Tyr Ser Val 1140
Leu Val Val Ala Lys Val Glu 1145 1150	Lys Gly Lys Ser	Lys Lys Leu Lys 1155
Ser Val Lys Glu Leu Leu Gly 1160 1165	Ile Thr Ile Met	Glu Arg Ser Ser 1170
Phe Glu Lys Asn Pro Ile Asp 1175 1180	Phe Leu Glu Ala	Lys Gly Tyr Lys 1185
Glu Val Lys Lys Asp Leu Ile 1190 1195	Ile Lys Leu Pro	Lys Tyr Ser Leu 1200
Phe Glu Leu Glu Asn Gly Arg 1205 1210	Lys Arg Met Leu	Ala Ser Ala Gly 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 cagaauucgc	240
uaccugcagg aaaucuucag caacgaaaug gcaaaggucg acgacagcuu cuuccacaga	300
cuggaagaaa gcuuccuggu cgaagaagac aagaagcacg aaagacaccg 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 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 aguucaucaa 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
agauucgcau ggaugacaag aaagagcgaa gaaacaauca caccguggaa 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	aggauggggga	1980
agacugagca	gaaagcugau	caacggaauc	agagacaagc	agagcggaaa	gacaauccug	2040
gacuuccuga	agagcgacgg	auucgcaaac	agaaacuuca	ugcagcugau	ccacgacgac	2100
agccugacau	ucaaggaaga	cauccagaag	gcacagguca	gcfgacaggg	agacagccug	2160
cacgaacaca	ucgcaaaccu	ggcaggaagc	ccggcaauca	agaagggaau	ccugcagaca	2220
gucaaggucg	ucgacgaacu	ggucaagguc	augggaagac	acaagccgga	aaacaucguc	2280
aucgaaaugg	caagagaaaa	ccagacaaca	cagaaggggac	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	gaggaaagag	cgacaacguc	ccgagcgaag	aagucgucaa	gaagaugaag	2640
aacuacugga	gacagcugcu	gaacgcaaag	cugaucacac	agagaaaguu	cgacaaccug	2700
acaaaggcag	agagaggagg	acugagcgaa	cuggacaagg	caggauucau	caagagacag	2760
cuggucgaaa	caagacagau	cacaaagcac	gucgcacaga	uccuggacag	cagaaugaac	2820
acaaaguacg	acgaaaacga	caagcugauc	agagaaguca	aggucaucac	acugaagagc	2880
aagcugguca	gcgacuucag	aaaggacuuc	caguucuaca	aggucagaga	aaucaacaac	2940
uaccaccacg	cacacgacgc	auaccugaac	gcagucgucg	gaacagcacu	gaucaagaag	3000
uacccgaagc	uggaaagcga	auucgucuac	ggagacuaca	aggucuacga	cgucagaaaag	3060

augaucgcaa agagcgaaca ggaaaucgga aaggcaacag caaaguacuu cuucuacagc	3120
aacaucauga acuucuuaa gacagaaauc acacuggcaa acggagaaau cagaaagaga	3180
ccgcugaucg aaacaaacgg agaaacagga gaaaucgucu 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 uggucgucgc aaaggucgaa aagggaaga gcaagaagcu gaagagcguc	3480
aaggaacugc ugggaaucac aaucauggaa agaagcagcu ucgaaaagaa cccgaucgac	3540
uuccuggaag caaagggaau caaggaaguc aagaaggacc ugaucauaa gcugccgaag	3600
uacagccugu ucgaacugga aaacggaaga aagagaaugc uggcaagcgc 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 aagcaciaag	4020
gaaguccugg acgcaacacu gauccaccag agcaucacag gacuguacga aacaagaau	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

gacaagaagu acagcaucgg acuggcaauc ggaacaaaca gcgucggaug ggcagucauc	60
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acagacgaau	acaagguccc	gagcaagaag	uucaaggucc	ugggaaacac	agacagacac	120
agcaucaaga	agaaccugau	cggagcacug	cuguucgaca	gcgagagaaac	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	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	cggaaaccug	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	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	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	acaaggucan	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	agggaauccu	gcagacaguc	2220
aaggucgucg	acgaacuggu	caaggucaug	ggaagacaca	agccggaaaa	caucgucauc	2280
gaaauggcaa	gagaaaacca	gacaacacag	aaggagacaga	agaacagcag	agaaagaau	2340
aagagaau	caaggaacug	ggaagccaga	uccugaagga	acacccgguc		2400
gaaaacacac	agcugcagaa	cgaaaagcug	uaccuguacu	accugcagaa	cggaagagac	2460
auguacgucg	accaggaacu	ggacaucaac	agacugagcg	acuacgacgu	cgaccacauc	2520
gucccgagaa	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	ucagagaaa	caacaacuac	2940
caccacgcac	acgacgcaua	ccugaacgca	gucgucggaa	cagcacugau	caagaaguac	3000
ccgaagcugg	aaagcgaauu	cgucuacgga	gacuacaagg	ucuacgacgu	cagaaagaug	3060
aucgcaaaga	gcgaacagga	aaucggaaa	gcaacagcaa	aguacuucuu	cuacagcaac	3120
aucaugaacu	ucuucaagac	agaaaucaca	cuggcaaacg	gagaaucag	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 acagcccgac agucgcgauac 3420
 agcguccugg ucgucgcaaa ggucgaaaag ggaaagagca agaagcugaa gagcguaag 3480
 gaacugcugg gaaucacaau cauggaaaga agcagcuucg aaaagaaccc gaucgacuuc 3540
 cuggaagcaa agggauacaa ggaagucaag aaggaccuga ucaucaagcu gccgaaguac 3600
 agccuguucg aacuggaaaa cggaagaaag agaaucgugg caagcgcagg 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
 gcagcauucaguacuucga cacaacauc gacagaaaga gauacacaag cacaaaggaa 4020
 guccuggacg caacacugau ccaccagagc aucacaggac uguacgaaac aagaaucgac 4080
 cugagccagc ugggaggaga cggaagcgga agcccgaaga agaagagaaa ggucgacgga 4140
 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
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 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> 229
 <211> 4179
 <212> ARN
 <213> Secuencia artificial

<220>
 <223> Sintético: ORF del ARNm de dCas9 que codifica la SEQ ID NO: 228 que usa
 codones de
 mínima uridina, con codones de inicio y parada

<400> 229
 auggacaaga aguacagcau cggacuggca aucggaacaa acagcgucgg augggcaguc 60
 aucacagacg aaucacaggu cccgagcaag aaguucaagg uccugggaaa cacagacaga 120
 cacagcauca agaagaaccu gaucggagca cugcuguucg acagcggaga aacagcagaa 180
 gcaacaagac ugaagagaac agcaagaaga agauacacaa gaagaaagaa cagaauucgc 240
 uaccugcagg aaauucucag 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	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	aguucaucaa	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	caccguggaa	cuucgaagaa	1440
gucgucgaca	agggagcaag	cgcacagagc	uucaucgaaa	gaaugacaaa	cuucgacaag	1500
aaccugccga	acgaaaaggu	ccugccgaag	cacagccugc	uguacgaaua	cuucacaguc	1560
uacaacgaac	ugacaaaggu	caaguacguc	acagaaggaa	ugagaaagcc	ggcauuccug	1620
agcgggagaac	agaagaaggc	aaucgucgac	cugcuguuca	agacaaacag	aaaggucaca	1680
gucaagcagc	ugaaggaaga	cuacuucaag	aagaucgaau	gcuucgacag	cgucgaaauc	1740
agcgggagucg	aagacagauu	caacgcaagc	cugggaacau	accacgaccu	gcugaagauc	1800
aucaaggaca	aggacuuccu	ggacaacgaa	gaaaacgaag	acauccugga	agacaucguc	1860
cugacacuga	cacuguucga	agacagagaa	augaucgaag	aaagacugaa	gacauacgca	1920
caccuguuucg	acgacaaggu	caugaagcag	cugaagagaa	gaagauacac	aggauuggga	1980
agacugagca	gaaagcugau	caacggaauc	agagacaagc	agagcggaaa	gacaauccug	2040
gacuuccuga	agagcgacgg	auucgcaaac	agaaacuuca	ugcagcugau	ccacgacgac	2100
agccugacau	ucaaggaaga	cauccagaag	gcacagguca	gcggacaggg	agacagccug	2160
cacgaacaca	ucgcaaaccu	ggcaggaagc	ccggcaauca	agaagggaau	ccugcagaca	2220
gucaaggucg	ucgacgaacu	ggucaagguc	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	cgucgacgca	2520
aucgucccg	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	cacaaagcac	gucgcacaga	uccuggacag	cagaaugaac	2820
acaaaguacg	acgaaaacga	caagcugauc	agagaaguca	aggucaucac	acugaagagc	2880
aagcugguca	gcgacuucag	aaaggacuuc	caguucuaca	aggucagaga	aaucaacaac	2940
uaccaccacg	cacacgacgc	auaccugaac	gcagucgucg	gaacagcacu	gaucaagaag	3000
uacccgaagc	uggaaagcga	auucgucuac	ggagacuaca	aggucuacga	cgucagaaaag	3060
augaucgcaa	agagcgaaca	ggaaaucgga	aaggcaacag	caaaguacuu	cuucuacagc	3120
aacaucauga	acuucuucua	gacagaaauc	acacuggcaa	acggagaaaau	cagaaagaga	3180
ccgcugaucg	aaacaaacgg	agaaacagga	gaaaucgucu	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	ugggaauca	aaucauggaa	agaagcagcu	ucgaaaagaa	cccgaucgac	3540
uuccuggaag	caaagggaua	caaggaaguc	aagaaggacc	ugaucauca	gcugccgaag	3600
uacagccugu	ucgaacugga	aaacggaaga	aagagaaugc	uggcaagcgc	aggagaacug	3660
cagaagggaa	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 aagcaciaaag	4020
gaaguccugg acgcaacacu gauccaccag agcaucacag gacuguacga aacaagaauc	4080
gaccugagcc agcuggggagg agacggaagc ggaagcccga agaagaagag aaaggucgac	4140
ggaagcccga agaagaagag aaaggucgac agcggauag	4179

<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	
gacaagaagu acagcaucgg acuggcaauc ggaacaaaca gcgucggaug ggcagucauc	60
acagacgaau acaaggucc gagcaagaag uucaaggucc ugaggaaacac agacagacac	120
agcaucaaga agaaccugau cggagcacug cuguucgaca gcggagaaac agcagaagca	180
acaagacuga agagaacagc aagaagaaga uacacaagaa gaaagaacag aaucugcuac	240
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<213> Secuencia artificial

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<223> Sintético: Promotor T7

<400> 231
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<210> 232
<211> 50
<212> ADN
<213> Homo sapiens

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<221> misc_característica
<222> (1)..(50)
<223> Beta-globina humana 5 UTR

<400> 232
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<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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tatttttcatt gc 132

<210> 234
<211> 66
<212> ADN
<213> Homo sapiens

<220>
 <221> misc_característica
 <222> (1)..(66)
 <223> Alfa-globina humana 5 UTR

 <400> 234
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 cccacc 66

<210> 235
 <211> 110
 <212> ADN
 <213> Homo sapiens

<220>
 <221> misc_característica
 <222> (1)..(110)
 <223> Alfa-globina humana 3 UTR

 <400> 235
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 ttcctgcacc cgtacccccg tggctcttga ataaagtctg agtgggcggc 110

<210> 236
 <211> 29
 <212> ADN
 <213> Xenopus laevis

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 <221> misc_característica
 <222> (1)..(29)
 <223> beta-globina 5 UTR de Xenopus laevis

 <400> 236
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<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 thtagccatt cgtatctgct cctaataaaa agaaagtttc 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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<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 ctttcctaat aaaatgagga 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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<210> 241
 <211> 61
 <212> ADN
 <213> Secuencia artificial

<220>
 <223> Sintético: HSD17B4 5 UTR

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

<220>
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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> 242
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 cguaaucaac uugaaaaagu ggcaccgagu cgugcuuuu 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
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4405

<210> 245

<211> 4188

<212> ADN

<213> Secuencia artificial

<220>

<223> Sintético: ORF de Cas9 alternativo con 19.36 % de contenido de U

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gcgacccggc tcaaacgtac cgcgaggcga cgctacaccc ggcggaagaa tcgcatctgc 240

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ctggaagaat ctttcctggt ggaggaggac aagaagcatg aacggcatcc tatctttgga 360

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gatctgtcgc agctgggtgg cgatgggtggc ggtggatcct acccatacga cgtgcctgac	4140
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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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cgtgggttgg gcagtgatca cggatgaata caaagtgccg tccaagaagt tcaaggtcct	180
ggggaacacc gatagacaca gcatcaagaa gaatctcatc ggagccctgc tgtttgactc	240
cggcgaaacc gcagaagcga cccggctcaa acgtaccgcg aggcgacgct acaccggcg	300
gaagaatcgc atctgctatc tgcaagaaat cttttcgaac gaaatggcaa aggtggacga	360
cagcttcttc caccgcctgg aagaatcttt cctgggtggag gaggacaaga agcatgaacg	420
gcatcctatc tttggaaaca tcgtggacga agtggcgtag cacgaaaagt acccgaccat	480
ctaccatctg cggaagaagt tggttgactc aactgacaag gccgacctca gattgatcta	540
cttggccctc gcccatatga tcaaattccg cggacacttc ctgatcgaag gcgatctgaa	600
ccctgataac tccgacgtgg ataagctgtt cattcaactg gtgcagacct acaaccaact	660
gttcgaagaa aacccaatca atgccagcgg cgtcgatgcc aaggccatcc tgtccgcccg	720
gctgtcgaag tcgcggcgcc tcgaaaacct gatcgcacag ctgccgggag agaagaagaa	780
cggacttttc ggcaacttga tcgctctctc actgggactc actcccaatt tcaagtccaa	840
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ggacaatttg ctggcacaaa ttggcgatca gtacgcggat ctgttccttg ccgctaagaa	960
cctttcggac gcaatcttgc tgtccgatat cctgcgcgtg aacaccgaaa taaccaaagc	1020
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caaagcgctc gtgagacagc aactgcctga aaagtacaag gagattttct tcgaccagtc	1140
caagaatggg tacgcagggt acatcgatgg aggcgccagc caggaagagt tctataagtt	1200
catcaagcca atcctggaaa agatggacgg aaccgaagaa ctgctggtca agctgaacag	1260
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tctgggtgag ctgcacgcca tcttgcggcg ccaggaggac ttttaccat tcctcaagga	1380
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ttggaatttc gaggaagttg tggataaggg agcttcggca caatccttca tcgaacgaat	1560
gaccaacttc gacaagaatc tcccaaacga gaaggtgctt cctaagcaca gcctccttta	1620

cgaatacttc actgtctaca acgaactgac taaagtgaag tacgttactg aaggaatgag	1680
gaagccggcc tttctgagcg gagaacagaa gaaagcgatt gtcgatctgc tgttcaagac	1740
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cctggaagat atcgtcctga ccttgaccct tttcgaggat cgcgagatga tcgaggagag	1980
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cggtaaaact atcctggatt tcctcaaact ggatggcttc gctaatacgta acttcatgca	2160
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gaactccgc gaaaggatga agcggatcga agaaggaatc aaggagctgg gcagccagat	2460
cctgaaagag caccgggtgg aaaacacgca gctgcagaac gagaagctct acctgtacta	2520
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gattaccctg aaaagcaaac ttgtgtcgga ctttcggaag gactttcagt tttaaaagt	3000
gagagaaatc aacaactacc atcacgcgca tgacgcatac ctcaacgtg tggtcggcac	3060
cgccctgatc aagaagtacc ctaaacttga atcggagttt gtgtacggag actacaaggt	3120
ctacgacgtg aggaagatga tagccaagtc cgaacaggaa atcgggaaag caactgcgaa	3180
atacttcttt tactcaaaca tcatgaactt cttcaagact gaaattacgc tggccaatgg	3240

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aaatggaaag 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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caccgataga cacagcatca agaagaatct catcggagcc ctgctgtttg actccggcga	240
aaccgcagaa gcgacccggc tcaaacgtac cgcgaggcga cgctacacc ggcggaagaa	300
tcgcatctgc tatctgcaag aaatcttttc gaacgaaatg gcaaagggtg acgacagctt	360
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tatctttgga aacatcgtgg acgaagtggc gtaccacgaa aagtaccga ccatctacca	480
tctgcggaag aagttggtt actcaactga caaggccgac ctgagattga tctacttggc	540
cctcgcccat atgatcaaat tccgcggaca cttcctgatc gaaggcgatc tgaaccctga	600
taactccgac gtggataagc tgttcattca actggtgcag acctacaacc aactgttcga	660
agaaaacca atcaatgcca gcggcgtcga tgccaaggcc atcctgtccg cccggctgtc	720
gaagtcgcgg cgcctcgaaa acctgatcgc acagctgccg ggagagaaga agaacggact	780
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aaagaacctc gag	4453

<210> 248

<400> 248
000

<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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aatcgggctg gatatcgga ctaattccgt gggttgggca gtgatcacgg atgaatacaa	180
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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
ctggaagaaa gcttcctggt cgaagaagac aagaagcacg aaagacaccc gatcttcgga	360
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gacctgagcc agctgggagg agacggagga ggaagccga agaagaagag aaaggtctag	4140

<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

<400> 251

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gggaaacaca gacagacaca gcatcaagaa gaacctgatc ggagcactgc tgttcgacag	240
cggagaaaca gcagaagcaa caagactgaa gagaacagca agaagaagat acacaagaag	300

aaagaacaga atctgctacc tgcaggaaat cttcagcaac gaaatggcaa aggtcgacga	360
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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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cagatcggcg accagtacgc cgacctgttc ctggccgcca agaacctgag cgacgccatc	900
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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 N0: 252, secuencia de Kozak, y 3 UTR de ALB

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gggcaacacc gacagacaca gcatcaagaa gaacctgatc ggcgccctgc tgttcgacag	240
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aaagaacaga atctgctacc tgcaggagat cttcagcaac gagatggcca aggtggacga	360
cagcttcttc cacagactgg aggagagctt cctggtggag gaggacaaga agcacgagag	420
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cctggccctg gccacatga tcaagttcag aggccacttc ctgatcgagg gcgacctgaa	600
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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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ctagaagaaa gcttcctagt agaagaagac aaaaaacacg aacgacacc gatattcggg	360
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<210> 255
 <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

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gccgctaagc gcgagcatga taaaacgata cgacgaacac caccaagacc taacgctact	1080
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caaaaacggg tacgcgggggt acatagacgg gggggcgagc caagaagaat tctacaaatt	1200

cataaaaccg atactagaaa aaatggacgg gacggaagaa ctactagtaa aactaaaccg	1260
agaagacctt ctacgaaaac aacgaacgtt cgacaacggg agcataccgc accaaataca	1320
cctaggggaa ctacacgcga tactacgacg acaagaagac ttctaccgt tcctaaaaga	1380
caaccgagaa aaaatagaaa aaataactaac gttccgaata ccgtactacg tagggccgct	1440
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gacgaacttc gacaaaaacc taccgaacga aaaagtacta ccgaaacaca gcctactata	1620
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gaaccgaaaa gtaacggtaa aacaactaaa agaagactac ttcaaaaaaa tagaatgctt	1800
cgacagcgta gaaataagcg gggtagaaga ccgattcaac gcgagcctag ggacgtacca	1860
cgacctacta aaaataataa aagacaaaga cttcctagac aacgaagaaa acgaagacat	1920
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actaaaaacg tacgcgcacc tattcgacga caaagtaatg aaacaactaa aacgacgacg	2040
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cgggaaaacg atactagact tcctaaaaag cgacgggttc gcgaaccgaa acttcatgca	2160
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accggaaaac atagtaatag aaatggcgcg agaaaaccaa acgacgcaa aagggcacaaa	2400
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gttcataaaa cgacaactag tagaaacgcg acaaataacg aaacacgtag cgcaaatact	2880
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aacgaaccta ggggcgccgg cggcgttcaa atacttcgac acgacgatag accgaaaacg	4080
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 tctttttcgt tgggtgtaaag	4320
ccaacaccct gtctaaaaaa cataaatttc tttaatcatt 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 CleanCap™, 5 UTR de HSD, ORF correspondiente a la SEQ ID NO: 204, Secuencia de Kozak, y 3 UTR de ALB

<400> 256
agggtcccgca gtcggcgtcc agcggctctg cttgttcgtg tgtgtgtcgt tgcaggcctt 60
attcggatcc gccaccatgg acaagaagta cagcatcgga ctggacatcg gaacaaacag 120
cgtcggatgg gcagtcatca cagacgaata caaggtcccg agcaagaagt tcaaggctct 180
gggaaacaca gacagacaca gcatcaagaa gaacctgac ggagcactgc tgttcgacag 240
cggagaaaca gcagaagcaa caagactgaa gagaacagca agaagaagat acacaagaag 300
aaagaacaga atctgctacc tgcaggaaat cttcagcaac gaaatggcaa aggtcgacga 360
cagcttcttc cacagactgg aagaaagctt cctggtcgaa gaagacaaga agcacgaaag 420
acacccgatc ttcggaacaa 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
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ggacaacctg ctggcacaga tcggagacca gtacgcagac ctgttccttg cagcaaagaa 960
cctgagcgac gcaatcctgc tgagcgacat cctgagagtc aacacagaaa tcacaaaggc 1020
accgctgagc gcaagcatga tcaagagata cgacgaacac caccaggacc tgacactgct 1080
gaaggcactg gtcagacagc agctgccgga aaagtacaag gaaatcttct tcgaccagag 1140
caagaacgga tacgcaggat acatcgacgg aggagcaagc caggaagaat tctacaagtt 1200
catcaagccg atcctggaaa agatggacgg aacagaagaa ctgctgggtca agctgaacag 1260

agaagacctg ctgagaaagc agagaacatt cgacaacgga agcatcccgc accagatcca	1320
cctggggagaa ctgcacgcaa tcctgagaag acaggaagac ttctacccgt tcctgaagga	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 ttcttgagcg gagaacagaa gaaggcaatc gtcgacctgc tgttcaagac	1740
aaacagaaaag gtcacagtca agcagctgaa ggaagactac ttcaagaaga tcgaatgctt	1800
cgacagcgtc gaaatcagcg gagtcgaaga 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
cggaagaca atcctggact tcctgaagag cgacggattc gcaaacagaa acttcatgca	2160
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gccggaaaac atcgtcatcg aaatggcaag agaaaaccag acaacacaga agggacagaa	2400
gaacagcaga gaaagaatga agagaatcga agaaggaatc aaggaactgg gaagccagat	2460
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cctgcagaac ggaagagaca tgtacgtcga ccaggaactg gacatcaaca gactgagcga	2580
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attcatcaag agacagctgg tcgaaacaag acagatcaca aagcacgtcg cacagatcct	2880

ggacagcaga atgaacacaa agtacgacga aaacgacaag ctgatcagag aagtcaaggt	2940
catcacactg aagagcaagc tggtcagcga cttcagaaag 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 gaagtccaga caggaggatt cagcaaggaa agcatcctgc cgaagagaaa	3420
cagcgacaag ctgatcgcaa gaaagaagga ctgggacccg aagaagtacg gaggattcga	3480
cagcccgaca gtcgcataca gcgtcctggg cgtcgcaaag gtcgaaaagg gaaagagcaa	3540
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gaagagaaaag gtctagctag ccatcacatt taaaagcatc tcagcctacc atgagaataa	4260
gagaaagaaa atgaagatca atagcttatt catctctttt tctttttcgt tgggtgtaaag	4320
ccaacaccct gtctaaaaaa cataaatttc tttaatcatt ttgcctcttt tctctgtgct	4380
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<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

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gactcaccgt ccttgacacg gccaccatgg acaagaagta cagcatcgga ctggacatcg	180
gaacaaacag cgtcggatgg gcagtcatca cagacgaata caaggtcccg agcaagaagt	240
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tgttcgacag cggagaaaca gcagaagcaa caagactgaa gagaacagca agaagaagat	360
acacaagaag aaagaacaga atctgctacc tgcaggaaat cttcagcaac gaaatggcaa	420
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agcacgaaag acacccgatc ttcggaaaca tcgtcgacga agtcgcatac cacgaaaagt	540
acccgacaat ctaccacctg agaaagaagc tggtcgacag cacagacaag gcagacctga	600
gactgatcta cctggcactg gcacacatga tcaagttcag aggacacttc ctgatcgaag	660
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acaaccagct gttcgaagaa aacccgatca acgcaagcgg agtcgacgca aaggcaatcc	780
tgagcgcaag actgagcaag agcagaagac tggaaaacct gatcgcacag ctgccgggag	840
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tcgaccagag caagaacgga tacgcaggat acatcgacgg aggagcaagc caggaagaat	1260
tctacaagtt catcaagccg atcctggaaa agatggacgg aacagaagaa ctgctggtca	1320

agctgaacag agaagacctg ctgagaaagc agagaacatt cgacaacgga agcatcccg	1380
accagatcca cctgggagaa ctgcacgcaa tcctgagaag acaggaagac ttctaccctg	1440
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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 cgacctgctg aagatcatca aggacaagga cttcctggac aacgaagaaa	1980
acgaagacat cctggaagac atcgtcctga cactgacact gttcgaagac agagaaatga	2040
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agagaagaag atacacagga tggggaagac tgagcagaaa gctgatcaac ggaatcagag	2160
acaagcagag cggaagaca atcctggact tcctgaagag cgacggattc gcaaacagaa	2220
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aggtcagcgg acagggagac agcctgcacg aacacatcg aaacctggca ggaagcccgg	2340
caatcaagaa gggaatcctg cagacagtca aggtcgtcga cgaactggtc aaggctatgg	2400
gaagacacaa gccggaaaac atcgtcatcg aaatggcaag agaaaaccag acaacacaga	2460
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gaagccagat cctgaaggaa caccgggtcg aaaacacaca gctgcagaac gaaaagctgt	2580
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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 cttcagaaaag gacttccagt	3060
tctacaaggt cagagaaaatc aacaactacc accacgcaca cgacgcatac ctgaacgcag	3120
tcgtcggAAC agcactgatac aagaagtacc cgaagctgga aagcgaattc gtctacggag	3180
actacaaggt ctacgacgtc agaaagatga tcgcaaagag cgaacaggaa atcggaagg	3240
caacagcaaa gtactttctt tacagcaaca tcatgaactt cttcaagaca gaaatcacac	3300
tggcaaacgg agaaatcaga aagagaccgc tgatcgaac aaacggagaa acaggagaaa	3360
tcgtctggga caagggaaga gacttcgcaa cagtcagaaa ggtcctgagc atgccgcagg	3420
tcaacatcgt caagaagaca gaagtccaga caggaggatt cagcaaggaa agcatcctgc	3480
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gaggattcga cagcccgaca gtcgcataca gcgtcctggg cgtcgcaaag gtcgaaaagg	3600
gaaagagcaa gaagctgaag agcgtcaagg aactgctggg aatcacaatc atggaaagaa	3660
gcagcttcga aaagaacccg atcgacttcc tggaagcaaa gggatacaag gaagtcaaga	3720
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gaatgctggc aagcgcagga gaactgcaga agggaaacga actggcactg ccgagcaagt	3840
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agatcagcga attcagcaag agagtcattc tggcagacgc aaacctggac aaggctctga	4020
gcgcatacaa caagcacaga gacaagccga tcagagaaca ggcagaaaac atcatccacc	4080
tggtcacact gacaaacctg ggagcaccgg cagcattcaa gtacttcgac acaacaatcg	4140
acagaaagag atacacaagc acaaaggaag tcctggacgc aacctgatac caccagagca	4200
tcacaggact gtacgaaaca agaatacgacc tgagccagct gggaggagac ggaggaggaa	4260
gcccgaagaa gaagagaaaag gtctagctag ccatcacatt taaaagcatc tcagcctacc	4320
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tgggtgtaaag ccaacaccct gtctaaaaaa cataaatttc tttaatcatt ttgcctcttt	4440
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<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

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ccaccatgga caagaagtac agcatcggac tggacatcgg aacaaacagc gtcggatggg	120
cagtcatcac agacgaatac aaggtcccga gcaagaagtt caaggtcctg ggaaacacag	180
acagacacag catcaagaag aacctgatcg gagcactgct gttcgacagc ggagaaacag	240
cagaagcaac aagactgaag agaacagcaa gaagaagata cacaagaaga aagaacagaa	300
tctgctacct gcaggaaatc ttcagcaacg aaatggcaaa ggtcgacgac agcttcttcc	360
acagactgga agaaagcttc ctgggtcgaag aagacaagaa gcacgaaaga caccgatctt	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 cgcaagcgga gtcgacgcaa aggcaatcct gagcgcaaga ctgagcaaga	720
gcagaagact ggaaaacctg atcgcacagc tgccgggaga aaagaagaac ggactgttcg	780
gaaacctgat cgactgagc ctgggactga caccgaactt caagagcaac ttcgacctgg	840
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caagcatgat caagagatac gacgaacacc accaggacct gacactgctg aaggcactgg	1080
tcagacagca gctgccggaa aagtacaagg aaatcttctt cgaccagagc aagaacggat	1140
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acagcagatt cgcattggatg acaagaaaga gcgaagaaac aatcacaccg tggaacttcg	1500
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aaatcagcgg agtcgaagac agattcaacg caagcctggg aacataccac gacctgtgta	1860
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acaactacca ccacgcacac gacgcatacc tgaacgcagt cgtcgggaaca gcactgatca	3060
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caaaggaagt cctggacgca aactgatcc accagagcat cacaggactg tacgaaacaa	4140
gaatcgacct gagccagctg ggaggagacg gaggaggaag cccgaagaag aagagaaagg	4200
tctagctagc gctcgctttc ttgctgtcca atttctatta aaggttcctt tgttccctaa	4260
gtccaactac taaactgggg gatattatga agggccttga gcattctggat tctgcctaata	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

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aggtcccgag caagaagttc aaggtcctgg gaaacacaga cagacacagc atcaagaaga	180
acctgatcgg agcactgctg ttcgacagcg gagaaacagc agaagcaaca agactgaaga	240
gaacagcaag aagaagatac acaagaagaa agaacagaat ctgctacctg caggaaatct	300
tcagcaacga aatggcaaag gtcgacgaca gcttcttcca cagactggaa gaaagcttcc	360
tggtcgaaga agacaagaag cacgaaagac acccgatctt cggaaacatc gtcgacgaag	420
tcgcatacca cgaaaagtac ccgacaatct accacctgag aaagaagctg gtcgacagca	480
cagacaaggc agacctgaga ctgatctacc tggcactggc acacatgatc aagttcagag	540
gacacttcct gatcgaagga gacctgaacc cggacaacag cgacgtcgac aagctgttca	600
tccagctggg ccagacatac aaccagctgt tcgaagaaaa cccgatcaac gcaagcggag	660
tcgacgcaaa ggcaatcctg agcgcaagac tgagcaagag cagaagactg gaaaacctga	720
tcgcacagct gccgggagaa aagaagaacg gactgttcgg aaacctgatc gcactgagcc	780
tgggactgac accgaacttc aagagcaact tcgacctggc agaagacgca aagctgcagc	840
tgagcaagga cacatacgac gacgacctgg acaacctgct ggacacagatc ggagaccagt	900
acgcagacct gttcctggca gcaaagaacc tgagcgacgc aatcctgctg agcgacatcc	960
tgagagtcaa cacagaaatc acaaaggcac cgctgagcgc aagcatgatc aagagatacg	1020
acgaacacca ccaggacctg aactgctga aggcactggg cagacagcag ctgccggaag	1080
agtacaagga aatcttcttc gaccagagca agaacggata cgcaggatac atcgacggag	1140
gagcaagcca ggaagaattc tacaagttca tcaagccgat cctggaaaag atggacggaa	1200
cagaagaact gctggtcaag ctgaacagag aagacctgct gagaaagcag agaacattcg	1260
acaacggaag catcccgcac cagatccacc tgggagaact gcacgcaatc ctgagaagac	1320
aggaagactt ctaccgcttc ctgaaggaca acagagaaaa gatcgaaaag atcctgacat	1380
tcagaatccc gtactacgtc ggaccgctgg caagaggaaa cagcagattc gcatggatga	1440
caagaaagag cgaagaaaca atcacaccgt ggaacttcga agaagtcgtc gacaagggag	1500

caagcgcaca	gagcttcatc	gaaagaatga	caaacttcga	caagaacctg	ccgaacgaaa	1560
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gattcaacgc	aagcctggga	acataccacg	acctgctgaa	gatcatcaag	gacaaggact	1860
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tcgaagacag	agaaatgatc	gaagaaagac	tgaagacata	cgcacacctg	ttcgacgaca	1980
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acctggcagg	aagcccggca	atcaagaagg	gaatcctgca	gacagtcaag	gtcgtcgacg	2280
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cagaaaacat catccacctg ttcacactga caaacctggg agcaccggca gcattcaagt	4020
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gaacacccga atggagtctc taagctacat aataccaact tacactttac aaaatgttgt	4260
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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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acctgatcgg agcactgctg ttcgacagcg gagaaacagc agaagcaaca agactgaaga	240
gaacagcaag aagaagatac acaagaagaa agaacagaat ctgctacctg caggaaatct	300
tcagcaacga aatggcaaag gtcgacgaca gcttcttcca cagactggaa gaaagcttcc	360
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cagacaaggc agacctgaga ctgatctacc tggcactggc acacatgac aagttcagag	540
gacacttcct gatcgaagga gacctgaacc cggacaacag cgacgtcgac aagctgttca	600
tccagctggg ccagacatac aaccagctgt tcgaagaaaa cccgatcaac gcaagcggag	660
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aggtcctgcc gaagcacagc ctgctgtacg aatacttcac agtctacaac gaactgacaa	1620

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cagaaaacat catccacctg ttcacactga caaacctggg agcaccggca gcattcaagt	4020
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<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

aggtcccga gtcggcgtcc agcggctctg cttgttcgtg tgtgtgtcgt tgcaggcctt	60
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attcggatcc gccaccatgg acaagaagta cagcatcgga ctggacatcg gaacaaacag	120
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cgtcggatgg gcagtcatca cagacgaata caaggtcccg agcaagaagt tcaaggtcct	180
gggaaacaca gacagacaca gcatcaagaa gaacctgatac ggagcactgc tgttcgacag	240
cggagaaaca gcagaagcaa caagactgaa gagaacagca agaagaagat acacaagaag	300
aaagaacaga atctgctacc tgcaggaaat cttcagcaac gaaatggcaa aggtcgacga	360
cagcttcttc cacagactgg aagaaagctt cctggtcgaa gaagacaaga agcacgaaag	420
acacccgatc ttcggaacaa tcgtcgacga agtcgcatac cacgaaaagt acccgacaat	480
ctaccacctg agaaagaagc tggtcgacag cacagacaag gcagacctga gactgatcta	540
cctggcactg gcacacatga tcaagttcag aggacacttc ctgatacgaag gagacctgaa	600
cccggacaac agcgacgtcg acaagctgtt catccagctg gtccagacat acaaccagct	660
gttcgaagaa aacccgatca acgcaagcgg agtcgacga aaggcaatcc tgagcgcaag	720
actgagcaag agcagaagac tggaaaacct gatcgacag ctgccgggag aaaagaagaa	780
cggactgttc ggaaacctga tcgcactgag cctgggactg acaccgaact tcaagagcaa	840
cttcgacctg gcagaagacg caaagctgca gctgagcaag gacacatac acgacgacct	900
ggacaacctg ctggcacaga tcggagacca gtacgcagac ctgttcctgg cagcaaagaa	960
cctgagcgac gcaatcctgc tgagcgacat cctgagagtc aacacagaaa tcacaaaggc	1020
accgctgagc gcaagcatga tcaagagata cgacgaacac caccaggacc tgacactgct	1080
gaaggcactg gtcagacagc agctgccgga aaagtacaag gaaatcttct tcgaccagag	1140
caagaacgga tacgcaggat acatcgacgg aggagcaagc caggaagaat tctacaagtt	1200
catcaagccg atcctggaaa agatggacgg aacagaagaa ctgctggtca agctgaacag	1260
agaagacctg ctgagaaagc agagaacatt cgacaacgga agcatcccgc accagatcca	1320
cctgggagaa ctgcacgcaa tcctgagaag acaggaagac ttctaccctg tcctgaagga	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 ttctgagcg gagaacagaa gaaggcaatc gtcgacctgc tgttcaagac	1740

aaacagaaag gtcacagtca agcagctgaa ggaagactac ttcaagaaga tcgaatgctt	1800
cgacagcgtc gaaatcagcg gagtcgaaga cagattcaac gcaagcctgg gaacatacca	1860
cgacctgctg aagatcatca aggacaagga cttcctggac aacgaagaaa acgaagacat	1920
cctggaagac atcgtcctga cactgacact gttcgaagac agagaaatga tcgaagaaag	1980
actgaagaca tacgcacacc tggttcgacga 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
acaggagac agcctgcacg aacacatcgc aaacctggca ggaagcccgg caatcaagaa	2280
gggaatcctg cagacagtca aggtcgtcga cgaactggtc 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 tcccgcagag cttcctgaag gacgacagca tcgacaacaa	2640
ggtcctgaca agaagcgaca agaacagagg aaagagcgac aacgtcccga gcgaagaagt	2700
cgtcaagaag atgaagaact actggagaca gctgctgaac gcaaagctga tcacacagag	2760
aaagttcgac aacctgacaa aggcagagag aggaggactg agcgaactgg acaaggcagg	2820
attcatcaag agacagctgg tcgaaacaag acagatcaca aagcacgtcg cacagatcct	2880
ggacagcaga atgaacacaa agtacgacga aaacgacaag ctgatcagag aagtcaaggt	2940
catcacactg aagagcaagc tggtcagcga cttcagaaag gacttccagt tctacaaggt	3000
cagagaaatc aacaactacc accacgcaca cgacgcatac ctgaacgcag tcgtcggaac	3060
agcactgatac aagaagtacc cgaagctgga aagcgaattc gtctacggag actacaaggt	3120
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 gcgtcctggg 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
aagcgcagga gaactgcaga agggaaacga actggcactg ccgagcaagt acgtcaactt	3780
cctgtacctg gcaagccact acgaaaagct gaagggaagc ccggaagaca acgaacagaa	3840
gcagctgttc gtcgaacagc acaagcacta cctggacgaa atcatcgaac agatcagcga	3900
attcagcaag agagtcattc tggcagacgc aaacctggac aaggtcctga gcgcatacaa	3960
caagcacaga gacaagccga tcagagaaca ggcagaaaac atcatccacc tgttcacact	4020
gacaaacctg ggagcaccgg cagcattcaa gtacttcgac acaacaatcg acagaaagag	4080
atacacaagc acaaaggaag tcctggacgc aacactgac caccagagca tcacaggact	4140
gtacgaaaca agaatcgacc tgagccagct gggaggagac ggaggaggaa gcccgaaaga	4200
gaagagaaag gtctagctag ccatcacatt taaaagcatc tcagcctacc atgagaataa	4260
gagaaagaaa atgaagatca atagcttatt catctctttt tctttttcgt tgggtgtaaag	4320
ccaacaccct gtctaaaaaa cataaatctt tttaatcatt ttgcctcttt tctctgtgct	4380
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
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aaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaa	93
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<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 ctcgatcaac 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 gtcctgcagg cagcaaactt cgacgaaaac 300
 ggactgatca agtcgctgcc gaacacaccg tggcagctga gagcagcagc actggacaga 360
 aagctgacac cgctggaatg gtcggcagtc ctgctgcacc tgatcaagca cagaggatac 420
 ctgtcgcaga gaaagaacga aggagaaaca gcagacaagg aactgggagc actgctgaag 480
 ggagtcgcag gaaacgcaca cgactgcag acaggagact tcagaacacc ggcagaactg 540
 gcactgaaca agttcgaaaa ggaatcggga cacatcagaa accagagatc ggactactcg 600
 cacacattct cgagaaagga cctgcaggca gaactgatcc tgctgttcga aaagcagaag 660
 gaattcggaa acccgcacgt ctcgggagga 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 acatctcggt cgacaagtgc	1260
gtccagatct cgctgaaggc actgagaaga atcgtcccgc tgatggaaca gggaaagaga	1320
tacgacgaag catgcgaga aatctacgga gaccactacg gaaagaagaa cacagaagaa	1380
aagatctacc tgccgccgat cccggcagac gaaatcagaa acccggtcgt cctgagagca	1440
ctgtcgcagg caagaaaggt catcaacgga gtcgtcagaa gatacggatc gccggcaaga	1500
atccacatcg aaacagcaag agaagtcgga aagtcgttca aggacagaaa ggaaatcgaa	1560
aagagacagg aagaaaacag aaaggacaga gaaaaggcag cagcaaagtt cagagaatac	1620
ttcccgaact tcgtcggaga accgaagtcg aaggacatcc tgaagctgag actgtacgaa	1680
cagcagcacg gaaagtcct gtactcggga aaggaaatca acctgggaag actgaacgaa	1740
aagggatacg tcgaaatcga ccacgcactg ccgttctcga gaacatggga cgactcgttc	1800
aacaacaagg tcctggctct gggatcggaa aaccagaaca agggaaacca gacaccgtac	1860
gaatacttca acggaaagga caactcgaga gaatggcagg aattcaaggc aagagtcgaa	1920
acatcgagat tcccagatc gaagaagcag agaatcctgc tgcagaagtt cgacgaagac	1980
ggattcaagg aaagaaacct gaacgacaca agatactca acagattcct gtgccagtgc	2040
gtcgcagaca gaatgagact gacaggaaag ggaaagaaga gagtcttcgc atcgaacgga	2100
cagatcacia acctgctgag aggattctgg ggactgagaa aggtcagagc agaaaacgac	2160
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atcacaagat tcgtcagata caaggaaatg aacgcattcg acggaaagac aatcgacaag	2280
gaaacaggag aagtcctgca ccagaagaca cacttcccgc agccgtggga attcttcgca	2340
caggaagtca tgatcagagt cttcggaaag ccggacggaa agccggaatt cgaagaagca	2400
gacacactgg aaaagctgag aacactgctg gcagaaaagc tgtcgtcgag accggaagca	2460
gtccacgaat acgtcacacc gctgttcgtc tcgagagcac cgaacagaaa gatgtcggga	2520

cagggacaca tggaaacagt caagtcggca aagagactgg acgaaggagt ctcggtcctg	2580
agagtccccgc tgacacagct gaagctgaag gacctggaaa agatgggtcaa cagagaaaaga	2640
gaaccgaagc tgtacgaagc actgaaggca agactggaag cacacaagga cgacccggca	2700
aaggcattcg cagaaccgtt ctacaagtac gacaaggcag gaaacagaac acagcaggtc	2760
aaggcagtca gagtccaaca ggtccagaag acaggagtct gggtcagaaa ccacaacgga	2820
atcgagaca acgcaacaat ggtcagagta gacgtcttcg aaaagggaga caagtactac	2880
ctgggtcccga tctactcgtg gcaggctgca aagggaatcc tgccggacag agcagtcgtc	2940
cagggaaaagg acgaagaaga ctggcagctg atcgacgact cgttcaactt caagttctcg	3000
ctgcacccga acgacctggt cgaagtcatt acaaagaagg caagaatgtt cggatacttc	3060
gcatcgtgcc acagaggaac aggaaacatc aacatcagaa tccacgacct ggaccacaag	3120
atcggaaaaga acggaatcct ggaaggaatc ggagtcaaga cagcactgtc gttccagaag	3180
taccagatcg acgaactggg aaaggaaatc agaccgtgca gactgaagaa gagaccgccg	3240
gtcagatccg gaaagagaac agcagacgga tcggaattcg aatcgccgaa gaagaagaga	3300
aaggtcgaat 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	
gcagcatca agccgaactc gatcaactac atcctgggac tggacatcgg aatcgcatcg	60
gtcggatggg caatgggtcga aatcgacgaa gaagaaaacc cgatcagact gatcgacctg	120
ggagtcaag tcttcgaaag agcagaagtc ccgaagacag gagactcgct ggcaatggca	180
agaagactgg caagatcggc cagaagactg acaagaagaa gagcacacag actgctgaga	240
acaagaagac tgctgaagag agaaggagtc ctgcaggcag caaacttcga cgaaaacgga	300
ctgatcaagt cgctgccgaa cacaccgtgg cagctgagag cagcagcact ggacagaaag	360

ctgacaccgc tggaatggtc ggcagtcctg ctgcacctga tcaagcacag aggatacctg	420
tcgcagagaa agaacgaagg agaaacagca gacaaggaac tgggagcact gctgaaggga	480
gtcgcaggaa acgcacacgc actgcagaca ggagacttca gaacaccggc agaactggca	540
ctgaacaagt tcgaaaagga atcgggacac atcagaaacc agagatcgga ctactcgcac	600
acattctcga gaaaggacct gcaggcagaa ctgacacctg 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 ggatcggaac 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
atcggaacag cattctcgct gttcaagaca gacgaagaca tcacaggaag actgaaggac	1200
agaatccagc cggaatcctt ggaagcactg ctgaagcaca tctcgttcga caagttcgtc	1260
cagatctcgc tgaaggcact gagaagaatc gtcccgtga tggaaacagg aaagagatac	1320
gacgaagcat gcgcagaaat ctacggagac cactacggaa agaagaacac agaagaaaag	1380
atctacctgc cgccgatccc ggcagacgaa atcagaaacc cggtcgtcct gagagcactg	1440
tcgcaggcaa gaaaggtcat caacggagtc gtcagaagat acggatcgcc ggcaagaatc	1500
cacatcgaaa cagcaagaga agtcggaaag tcgttcaagg acagaaagga aatcgaaaag	1560
agacaggaag aaaacagaaa ggacagagaa aaggcagcag caaagttcag agaatacttc	1620
ccgaacttcg tcggagaacc gaagtcgaag gacatcctga agctgagact gtacgaacag	1680
cagcacggaa agtgcctgta ctcgggaaag gaaatcaacc tgggaagact gaacgaaaag	1740
ggatacgtcg aaatcgacca cgcactgccg ttctcgagaa catgggacga ctcgttcaac	1800
aacaaggtcc tggctcctggg atcggaaaac cagaacaagg gaaaccagac accgtacgaa	1860
tacttcaacg gaaaggacaa ctcgagagaa tggcaggaat tcaaggcaag agtcgaaaca	1920
tcgagattcc cgagatcgaa gaagcagaga atcctgctgc agaagttcga cgaagacgga	1980

ttcaaggaaa gaaacctgaa cgacacaaga tacgtcaaca gattcctgtg ccagttcgtc	2040
gcagacagaa tgagactgac aggaaaggga aagaagagag tcttcgcatc gaacggacag	2100
atcaciaaacc tgctgagagg attctgggga ctgagaaagg tcagagcaga aaacgacaga	2160
caccacgcac tggacgcagt cgtcgtcgca tgctcgacag tcgcaatgca gcagaagatc	2220
acaagattcg tcagatacaa ggaaatgaac gcattcgacg gaaagacaat cgacaaggaa	2280
acaggagaag tcctgcacca gaagacacac ttcccgcagc cgtgggaatt cttcgcacag	2340
gaagtcatga tcagagtctt cggaaagccg gacggaaagc cggaattcga agaagcagac	2400
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cacgaatacg tcacaccgct gttcgtctcg agagcaccga acagaaagat gtcgggacag	2520
ggacacatgg aaacagtcaa gtcggcaaag agactggacg aaggagtctc ggtcctgaga	2580
gtcccgtga cacagctgaa gctgaaggac ctggaaaaga tgggtcaacag agaaagagaa	2640
ccgaagctgt acgaagcact gaaggcaaga ctggaagcac acaaggacga cccggcaaag	2700
gcattcgagc aaccgttcta caagtacgac 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 gcagctgacg gacgactcgt tcaacttcaa gttctcgctg	3000
cacccgaacg acctggctga agtcatacaca aagaaggcaa gaatgttcgg atacttcgca	3060
tcgtgccaca gaggaacagg aaacatcaac atcagaatcc acgacctgga ccacaagatc	3120
ggaaagaacg gaatcctgga aggaatcgga gtcaagacag cactgtcggt 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

gggagacca agctggctag cgtttaaact taagcttgga tccgccacca tggcagcatt	60
caagccgaac tcgatcaact acatcctggg actggacatc ggaatcgcac cggtcggatg	120
ggcaatggtc gaaatcgacg aagaagaaaa ccgatcaga 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 tcggcagtcc tgctgcacct gatcaagcac agaggatacc tgtcgcagag	480
aaagaacgaa ggagaaacag cagacaagga actgggagca ctgctgaagg gagtgcagg	540
aaacgcacac gcactgcaga caggagactt cagaacaccg gcagaactgg cactgaacaa	600
gttcgaaaag gaatcgggac acatcagaaa ccagagatcg gactactcgc acacattctc	660
gagaaaggac ctgcaggcag aactgatcct gctgttcgaa aagcagaagg aattcggaaa	720
cccgcacgtc tcgggaggac tgaaggaagg aatcgaaaca ctgctgatga cacagagacc	780
ggcactgtcg ggagacgcag tccagaagat gctgggacac tgcacattcg aaccggcaga	840
accgaaggca gcaaagaaca catacacagc agaaagattc atctggctga caaagctgaa	900
caacctgaga atcctggaac agggatcgga aagaccgctg acagacacag aaagagcaac	960
actgatggac gaaccgtaca gaaagtcgaa gctgacatac gcacaggcaa gaaagctgct	1020
gggactggaa gacacagcat tcttcaaggg actgagatac ggaaaggaca acgcagaagc	1080
atcgacactg atggaaatga aggcatacca cgcaatctcg agagcactgg aaaaggaagg	1140
actgaaggac aagaagtcgc cgctgaacct gtcgccgga ctgcaggacg aaatcggaac	1200
agcattctcg ctgttcaaga cagacgaaga catcacagga agactgaagg acagaatcca	1260
gccggaaatc ctggaagcac tgctgaagca catctcgttc gacaagtctg tccagatctc	1320
gctgaaggca ctgagaagaa tcgtcccgct gatggaacag ggaaagagat acgacgaagc	1380
atgcgagaa atctacggag accactacgg aaagaagaac acagaagaaa agatctacct	1440
gccgccgatc ccggcagacg aaatcagaaa ccgggtcgtc ctgagagcac tgtcgcaggc	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
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cgaaatcgac cacgcactgc cgttctcgag aacatgggac gactcgttca acaacaaggt	1860
cctggtcctg ggatcggaaa accagaacaa gggaaaccag acaccgtacg aatacttcaa	1920
cggaaaggac aactcgagag aatggcagga attcaaggca agagtcgaaa catcgagatt	1980
cccgagatcg aagaagcaga gaatcctgct gcagaagttc gacgaagacg gattcaagga	2040
aagaaacctg aacgacacaa gatacgtcaa cagattcctg tgccagttcg tcgcagacag	2100
aatgagactg acaggaaagg gaaagaagag agtcttcgca tcgaacggac agatcacaaa	2160
cctgctgaga ggattctggg gactgagaaa ggtcagagca gaaaacgaca gacaccacgc	2220
actggacgca gtcgtcgtcg catgctcgac agtcgcaatg cagcagaaga tcacaagatt	2280
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aaagctgaga acactgctgg cagaaaagct gtcgtcgaga ccggaagcag tccacgaata	2520
cgtcacaccg ctgttcgtct cgagagcacc gaacagaaag atgtcgggac agggacacat	2580
ggaaacagtc aagtcggcaa agagactgga cgaaggagtc tcggtcctga gagtcccgt	2640
gacacagctg aagctgaagg acctggaaaa gatggtcaac agagaaaagag aaccgaagct	2700
gtacgaagca ctgaaggcaa gactggaagc acacaaggac gacccggcaa aggcattcgc	2760
agaaccgttc tacaagtacg acaaggcagg aaacagaaca cagcaggtca aggcagtcag	2820
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cgcaacaatg gtcagagtag acgtcttcga aaaggagac aagtactacc tggtcccgat	2940
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cgaagaagac tggcagctga tcgacgactc gttcaacttc aagttctcgc tgcacccgaa	3060
cgacctggtc gaagtcatca caaagaaggc aagaatgttc ggatacttcg catcgtgcca	3120

cagaggaaca ggaaacatca acatcagaat ccacgacctg gaccacaaga tcggaaagaa 3180
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 ccactccac tgtcctttcc taataaaatg aggaaattgc atgcattgt ctgagtaggt 3540
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<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 auagcaaguu aaaaauaggc 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
1 5

<210> 275
<211> 7
<212> PRT
<213> Secuencia artificial

<220>
<223> Sintético: NLS de SV40 alterno
<400> 275

Pro Lys Lys Lys Arg Arg Val
1 5

<210> 276
<211> 16
<212> PRT
<213> Secuencia artificial

<220>
<223> Sintético: NLS de nucleoplasmina

<400> 276

Lys Arg Pro Ala Ala Thr Lys Lys Ala Gly Gln Ala Lys Lys Lys Lys
1 5 10 15

<210> 277
<211> 10
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: secuencia de Kozak ejemplar

<400> 277
gccrccaugg

<210> 278
<211> 13
<212> ARN
<213> Secuencia artificial

<220>
<223> Sintético: secuencia de Kozak ejemplar

<400> 278
gccgccrcca ugg