

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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<222> (29)..(40)

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<210> 18

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<223> Sintético: ARNg CR003348 dirigido a TTR humana (Exón 2)

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<213> Secuencia artificial

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

<400> 32

gcaugggcuc acaacugagg 20

<210> 33

<211> 20

<212> ARN

<213> Secuencia artificial

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

<400> 33

acugaggagg aauuuguaga 20

<210> 34

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 34

cugaggagga auuuguagaa 20

<210> 35

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 35

uguagaaggg auauacaaag 20

<210> 36

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 36

aaauagacac caaauuuac 20

<210> 37

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 37

agacacaaa ucuuacugga

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<210> 38

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 38

aagugccuuc caguaagauu

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<210> 39

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 39

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<210> 40

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 40

ccucugcaug cucauggaau 20

<210> 41

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 41

accucugcau gcucauggaa 20

<210> 42

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 42

uacucaccuc ugcaugcuca 20

<210> 43

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 43

guauucacag ccaacgacuc 20

<210> 44

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 44

gcggcggggg ccggagucgu 20

<210> 45

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 45

aaugguguag cggcgggggc 20

<210> 46

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 46

cggcaauggu guagcggcgg 20

<210> 47

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 47

gcggcaaugg uguagcggcg 20

<210> 48

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 48

ggcggcaaug guguagcggc 20

<210> 49

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 49

gggcggcaau gguguagcgg

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<210> 50

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 50

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<210> 51

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 51

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<210> 52

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 52

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

auaggaguag gggcucagca 20

<210> 54

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 54

aauaggagua ggggcucagc 20

<210> 55

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 55

ccccuacucc uauuccacca 20

<210> 56

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 56

ccguggugga auaggaguag 20

<210> 57

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 57

gccguggugg aauaggagua

20

<210> 58

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 58

gacgacagcc gugguggaau

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<210> 59

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 59

auuggugacg acagccgugg 20

<210> 60

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 60

gggauuggug acgacagccg 20

<210> 61

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 61

ggcugucguc accaauccca

20

<210> 62

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 62

agucccucau uccuugggau

20

<210> 63

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 63

uccacucauu cuuggcagga

20

<210> 64

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 64

agccguggug gaauaggagu 20

<210> 65

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 65

ucacagaaac 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 ucuacaccca

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

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<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

aaaucuuacu ggaaggcacu 20

<210> 72

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

<223> Sintético: ARNg CR005307 dirigido a TTR humana (Exón 4)

<400> 72

ugucugucuu cucucauagg 20

<210> 73

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

<223> Sintético: ARNg CR000689 dirigido a TTR de cyno

<400> 73

acacaaauac caguccagcg 20

<210> 74

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

<223> Sintético: ARNg CR005364 dirigido a TTR de cyno

<400> 74

aaaggcugcu gaugagaccu 20

<210> 75

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

<223> Sintético: ARNg CR005365 dirigido a TTR de cyno

<400> 75

cauugacagc aggacugccu 20

<210> 76

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 76

auaccagucc agcgaggcag 20

<210> 77

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 77

ccaguccagc gaggcagagg 20

<210> 78

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 78

ccuccucugc cucgcuggac

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<210> 79

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 79

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20

<210> 80

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 80

acuugucuuc ucuauacca

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<210> 81

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 81

aagugacuuc caguaagauu 20

<210> 82

<211> 20

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 82

aaaaggcugc ugaugagacc 20

<210> 83

<400> 83

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<210> 84

<400> 84

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<210> 85

<400> 85

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<210> 86

<400> 86

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<210> 87

<211> 100

<212> ARN

<213> Secuencia artificial

<220>

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

<220>

<221> base_modificada

<222> (1)..(3)

<223> Enlace PS, nucleótido 2'-O-Me

<220>

<221> base_modificada

<222> (29)..(40)

<223> nucleótido 2'-O-Me

<220>

<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>

<221> base_modificada

<222> (69)..(96)

<223> nucleótido 2'-O-Me

<220>

<221> base_modificada

<222> (97)..(100)

<223> Enlace PS, nucleótido 2'-O-Me

<400> 88

ucuagaacuu ugaccaucag guuuuagagc uagaaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cgugucuuuu 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

cguaaucaac uugaaaaagu ggcaccgagu cggugcuuuu

100

<210> 90

<211> 100

<212> ARN

<213> Secuencia artificial

<220>

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

<220>

<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

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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>

<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

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<212> ARN

<213> Secuencia artificial

<220>

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

<220>

<221> base_modificada

<222> (1)..(3)

<223> Enlace PS, nucleótido 2'-O-Me

<220>

<221> base_modificada

<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

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<212> ARN

<213> Secuencia artificial

<220>

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

<220>

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<222> (1)..(3)

<223> Enlace PS, nucleótido 2'-O-Me

<220>

<221> base_modificada

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<223> nucleótido 2'-O-Me

<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

acacaaaac caguccagca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 94

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<212> ARN

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<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

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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> 94

uucuuuggca acuuaccag guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguaaucaac uugaaaaagu ggcaccgagu cggugcuuuu

100

<210> 95

<211> 100

<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

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<221> base_modificada

<222> (69)..(96)

<223> nucleótido 2'-O-Me

<220>

<221> base_modificada

<222> (97)..(100)

<223> Enlace PS, nucleótido 2'-O-Me

<400> 95

aaaguucuag augcuguccg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac 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

<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> 96

uuugaccauc agaggacacu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 97

<211> 100

<212> ARN

<213> Secuencia artificial

<220>

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

<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> 97

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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 98

<211> 100

<212> ARN

<213> Secuencia artificial

<220>

<223> Sintético: secuencia modificada de ARNsg G000491 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> 98

auaccagucc agcaaggcag guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 99

<211> 100

<212> ARN

<213> Secuencia artificial

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<223> Sintético: secuencia modificada de ARNsg G000492 dirigido a TTR humana

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<223> Enlace PS, nucleótido 2'-O-Me

<220>

<221> base_modificada

<222> (29)..(40)

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<220>

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<222> (69)..(96)

<223> nucleótido 2'-O-Me

<220>

<221> base_modificada

<222> (97)..(100)

<223> Enlace PS, nucleótido 2'-O-Me

<400> 99

cuucucuaca cccagggcac guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 100

<211> 100

<212> ARN

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<221> base_modificada

<222> (1)..(3)

<223> Enlace PS, nucleótido 2'-O-Me

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<222> (69)..(96)

<223> nucleótido 2'-O-Me

<220>

<221> base_modificada

<222> (97)..(100)

<223> Enlace PS, nucleótido 2'-O-Me

<400> 100

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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<223> Sintético: secuencia modificada de ARNsg G000494 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

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<222> (69)..(96)

<223> nucleótido 2'-O-Me

<220>

<221> base_modificada

<222> (97)..(100)

<223> Enlace PS, nucleótido 2'-O-Me

<400> 101

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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<223> Sintético: secuencia modificada de ARNsg G000495 dirigido a TTR humana

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<223> Enlace PS, nucleótido 2'-O-Me

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<221> base_modificada

<222> (69)..(96)

<223> nucleótido 2'-O-Me

<220>

<221> base_modificada

<222> (97)..(100)

<223> Enlace PS, nucleótido 2'-O-Me

<400> 102

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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<222> (1)..(3)

<223> Enlace PS, nucleótido 2'-O-Me

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<223> nucleótido 2'-O-Me

<220>

<221> base_modificada

<222> (69)..(96)

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<220>

<221> base_modificada

<222> (97)..(100)

<223> Enlace PS, nucleótido 2'-O-Me

<400> 103

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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<223> Sintético: secuencia modificada de ARNsg G000497 dirigido a TTR humana

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<222> (1)..(3)

<223> Enlace PS, nucleótido 2'-O-Me

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<221> base_modificada

<222> (69)..(96)

<223> nucleótido 2'-O-Me

<220>

<221> base_modificada

<222> (97)..(100)

<223> Enlace PS, nucleótido 2'-O-Me

<400> 104

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cguuaucaac uugaaaaagu ggcaccgagu cgugucuuuu 100

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<222> (1)..(3)

<223> Enlace PS, nucleótido 2'-O-Me

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<222> (29)..(40)

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<221> base_modificada

<222> (69)..(96)

<223> nucleótido 2'-O-Me

<220>

<221> base_modificada

<222> (97)..(100)

<223> Enlace PS, nucleótido 2'-O-Me

<400> 105

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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<223> Enlace PS, nucleótido 2'-O-Me

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<222> (29)..(40)

<223> nucleótido 2'-O-Me

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<222> (69)..(96)

<223> nucleótido 2'-O-Me

<220>

<221> base_modificada

<222> (97)..(100)

<223> Enlace PS, nucleótido 2'-O-Me

<400> 106

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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<222> (1)..(3)

<223> Enlace PS, nucleótido 2'-O-Me

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<222> (29)..(40)

<223> nucleótido 2'-O-Me

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<221> base_modificada

<222> (69)..(96)

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<221> base_modificada

<222> (97)..(100)

<223> Enlace PS, nucleótido 2'-O-Me

<400> 107

ccaguccagc aaggcagagg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 108

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<222> (1)..(3)

<223> Enlace PS, nucleótido 2'-O-Me

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<221> base_modificada

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<221> base_modificada

<222> (97)..(100)

<223> Enlace PS, nucleótido 2'-O-Me

<400> 108

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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu

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<210> 109

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<212> ARN

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

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<222> (1)..(3)

<223> Enlace PS, nucleótido 2'-O-Me

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<222> (69)..(96)

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<221> base_modificada

<222> (97)..(100)

<223> Enlace PS, nucleótido 2'-O-Me

<400> 109

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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<223> Enlace PS, nucleótido 2'-O-Me

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<222> (69)..(96)

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<222> (97)..(100)

<223> Enlace PS, nucleótido 2'-O-Me

<400> 110

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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<222> (1)..(3)

<223> Enlace PS, nucleótido 2'-O-Me

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<221> base_modificada

<222> (29)..(40)

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<221> base_modificada

<222> (69)..(96)

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<220>

<221> base_modificada

<222> (97)..(100)

<223> Enlace PS, nucleótido 2'-O-Me

<400> 111

cauugauggc aggacugccu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 112

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

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<222> (1)..(3)

<223> Enlace PS, nucleótido 2'-O-Me

<220>

<221> base_modificada

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<222> (69)..(96)

<223> nucleótido 2'-O-Me

<220>

<221> base_modificada

<222> (97)..(100)

<223> Enlace PS, nucleótido 2'-O-Me

<400> 112

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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<223> Enlace PS, nucleótido 2'-O-Me

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<222> (69)..(96)

<223> nucleótido 2'-O-Me

<220>

<221> base_modificada

<222> (97)..(100)

<223> Enlace PS, nucleótido 2'-O-Me

<400> 113

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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu

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<210> 114

<211> 100

<212> ARN

<213> Secuencia artificial

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<222> (1)..(3)

<223> Enlace PS, nucleótido 2'-O-Me

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<222> (69)..(96)

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<221> base_modificada

<222> (97)..(100)

<223> Enlace PS, nucleótido 2'-O-Me

<400> 114

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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<212> ARN

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<223> Sintético: secuencia modificada de ARNsg G000503 dirigido a TTR de cyno

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<222> (1)..(3)

<223> Enlace PS, nucleótido 2'-O-Me

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<221> base_modificada

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<222> (69)..(96)

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<222> (97)..(100)

<223> Enlace PS, nucleótido 2'-O-Me

<400> 115

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cguuaucaac uugaaaaagu ggcaccgagu cgugucuuuu 100

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<212> ARN

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<222> (69)..(96)

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<222> (97)..(100)

<223> Enlace PS, nucleótido 2'-O-Me

<400> 116

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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 117

<211> 100

<212> ARN

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<222> (1)..(3)

<223> Enlace PS, nucleótido 2'-O-Me

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<221> base_modificada

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<222> (97)..(100)

<223> Enlace PS, nucleótido 2'-O-Me

<400> 117

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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<223> Enlace PS, nucleótido 2'-O-Me

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<221> base_modificada

<222> (97)..(100)

<223> Enlace PS, nucleótido 2'-O-Me

<400> 118

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cguaaucaac uugaaaaagu ggcaccgagu cggugcuuuu

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<223> Enlace PS, nucleótido 2'-O-Me

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<222> (97)..(100)

<223> Enlace PS, nucleótido 2'-O-Me

<400> 119

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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<222> (97)..(100)

<223> Enlace PS, nucleótido 2'-O-Me

<400> 120

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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<223> Enlace PS, nucleótido 2'-O-Me

<400> 121

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cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<212> ARN

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<223> Sintético: secuencia modificada de ARNsg G000510 dirigido a TTR de cyno

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<222> (1)..(3)

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<222> (97)..(100)

<223> Enlace PS, nucleótido 2'-O-Me

<400> 122

acuugucuuc ucuauacca guuuuagagc uagaaaagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

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<212> ARN

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<223> Enlace PS, nucleótido 2'-O-Me

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<222> (97)..(100)

<223> Enlace PS, nucleótido 2'-O-Me

<400> 123

aagugacuuc caguaagauu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguaaucaac uugaaaaagu ggcaccgagu cggugcuuuu

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<210> 124

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<212> ARN

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<222> (1)..(3)

<223> Enlace PS, nucleótido 2'-O-Me

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<222> (69)..(96)

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<221> base_modificada

<222> (97)..(100)

<223> Enlace PS, nucleótido 2'-O-Me

<400> 124

uuacagccac gucuacagca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 125

<211> 80

<212> ARN

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

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ggcaccgagu cggugcuuuu 80

<210> 126

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<210> 198

<400> 198

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<210> 199

<400> 199

000

<210> 200

<400> 200

000

<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 atcgaacaa acagcgtcgg atgggcagtc	60
atcacagacg aatacaaggt cccgagcaag aagttcaagg tcctgggaaa cacagacaga	120
cacagcatca agaagaacct gatcggagca ctgctgttcg acagcggaga aacagcagaa	180
gcaacaagac tgaagagaac agcaagaaga agatacaca gaagaaagaa cagaatctgc	240
tacctgcagg aaatcttcag caacgaaatg gcaaaggctg acgacagctt cttccacaga	300
ctggaagaaa gtttcttggt cgaagaagac aagaagcacg aaagacccc gatcttcgga	360
aacatcgtcg acgaagtcgc ataccacgaa aagtaccgga caatctacca cctgagaaag	420
aagctggtcg acagcacaga caaggcagac ctgagactga tctacctggc actggcacac	480
atgatcaagt tcagaggaca cttcctgac gaaggagacc tgaaccgga caacagcgac	540
gtcgacaagc tgttcatcca gctggtccag acatacaacc agctgttcga agaaaacccg	600
atcaacgcaa gcggagtcga cgcaaaggca atcctgagcg caagactgag caagagcaga	660
agactggaaa acctgatcgc acagctgccg ggagaaaaga agaacggact gttcggaac	720
ctgatcgac tgagcctggg actgacaccg aacttcaaga gcaacttcga cctggcagaa	780

gagcгаагс тгсгсгсгс сaggacaca tacgacgacg acctggacaa cctgctggca 840

cagatcggag accagtacgc agacctgttc ctggcagcaa agaacctgag cgacgcaatc 900

ctgctgagcg acatcctgag agtcaacaca gaaatcacia aggcaccgct gagcgcaagc 960

atgatcaaga gatacgacga acaccaccag gacctgacac tgctgaaggc actggtcaga 1020

cagcagctgc cggaaaagta caaggaaatc ttcttcgacc agagcaagaa cggatacgca 1080

ggatacatcg acggaggagc aagccaggaa gaattctaca agttcatcaa gccgatcctg 1140

gaaaagatgg acggaacaga 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 acgaaaaggt cctgccgaag cacagcctgc tgtacgaata cttcacagtc 1560

tacaacgaac tgacaaaggt caagtacgtc acagaaggaa tgagaaaagcc ggcattcctg 1620

agcggagaac agaagaaggc aatcgtcgac ctgctgttca agacaaacag aaaggtcaca 1680

gtcaagcagc tgaaggaaga ctacttcaag aagatcgaat gcttcgacag cgtcgaaatc 1740

agcggagtgc aagacagatt caacgcaagc ctgggaacat accacgacct gctgaagatc 1800

atcaaggaca aggacttctt ggacaacgaa gaaaacgaag acatcctgga agacatcgtc 1860

ctgacactga cactgttcga agacagagaa atgatcgaag aaagactgaa gacatacgca 1920

cacctgttcg acgacaaggt catgaagcag ctgaagagaa gaagatacac aggatgggga 1980

agactgagca gaaagctgat caacggaatc agagacaagc agagcggaaa gacaatcctg 2040

gacttcctga agagcgacgg attcgcaaac agaaacttca tgcagctgat ccacgacgac 2100

agcctgacat tcaaggaaga catccagaag gcacaggtca gcggacaggg agacagcctg 2160

cacgaacaca tcgcaaactt ggcaggaagc ccggcaatca agaagggaat cctgcagaca 2220

gtcaaggtcg tcgacgaact ggtcaaggtc atgggaagac acaagccgga aaacatcgtc 2280

atcgaaatgg caagagaaaa ccagacaaca cagaagggac agaagaacag cagagaaaga 2340

atgaagagaa tcgaagaagg aatcaaggaa ctgggaagcc agatcctgaa ggaacaccg 2400

gtcgaaaaca cacagctgca gaacgaaaag ctgtacctgt actacctgca gaacggaaga 2460

gacatgtacg tcgaccagga actggacatc aacagactga gcgactacga cgtcgaccac 2520

atcgccccg 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

ctggtcgaaa caagacagat cacaagcac gtcgcacaga tcctggacag cagaatgaac 2820

acaaagtacg acgaaaacga caagctgac agagaagtca aggtcatcac actgaagagc 2880

aagctggtca gcgacttcag aaaggacttc cagttctaca aggtcagaga aatcaacaac 2940

taccaccag cacacgacgc atacctgaac gcagtcgtcg gaacagcact gatcaagaag 3000

tacccgaagc tggaaagcga attcgtctac ggagactaca aggtctacga cgtcagaaag 3060

atgatcgcaa agagcgaaca ggaaatcgga aaggcaacag caaagtactt cttctacagc 3120

aacatcatga acttcttcaa gacagaaatc aactggcaa acggagaaat cagaaagaga 3180

ccgctgatcg aaacaaacgg agaaacagga gaaatcgtct gggacaaggg aagagacttc 3240

gcaacagtca gaaaggtcct gagcatgccg caggtaaca tcgtcaagaa gacagaagtc 3300

cagacaggag gattcagcaa ggaaagcatc ctgccgaaga gaaacagcga caagctgac 3360

gcaagaaaga aggactggga cccgaagaag tacggaggat tcgacagccc gacagtcgca 3420

tacagcgtcc tggctgctgc aaaggtcgaa aagggaaaga gcaagaagct gaagagcgtc 3480

aaggaactgc tgggaatcac aatcatggaa agaagcagct tcgaaaagaa cccgatcgac 3540

ttcctggaag caaagggata caaggaagtc aagaaggacc tgatcatcaa gctgccgaag 3600

tacagcctgt tcgaactgga aaacggaaga aagagaatgc tggcaagcgc aggagaactg 3660

cagaagggaa acgaactggc actgccgagc aagtacgtca acttcctgta cctggcaagc 3720

cactacgaaa agctgaaggg aagcccgga gacaacgaac agaagcagct gttcgtcgaa 3780

cagcacaagc actacctgga cgaaatcatc gaacagatca gcgaattcag caagagagtc 3840

atcctggcag acgcaaacct ggacaaggtc ctgagcgcat 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 ctgctgttg actccggcga aaccgcagaa 180

gcgacccggc tcaaactac cgcgaggcga cgctacacc ggcggaagaa tcgcatctgc 240

tatctgcaag agatcttttc gaacgaaatg gcaaaggtcg acgacagctt cttccaccgc 300

ctggaagaat ctttcttgtt ggaggaggac aagaagcatg aacggcatcc tatctttgga 360

aacatcgtcg acgaagtggc gtaccacgaa aagtaccga ccatctacca tctgcggaag 420

aagttggtg actcaactga caaggccgac ctgagattga tctacttggc cctcgcccat 480

atgatcaaat tccgcggaca cttctgatc gaaggcgatc tgaaccctga taactccgac 540

gtggataagc ttttcattca actggtgcag acctacaacc aactgttcga agaaaaccca 600

atcaatgcta gcggcgtcga tgccaaggcc atcctgtccg cccggctgtc gaagtcgcgg 660

cgctcgaaa acctgatcg acagctgccg ggagagaaaa agaacggact ttctggcaac 720

ttgatcgctc tctcactggg actcactccc aatttcaagt ccaattttga cctggccgag 780

gacgcgaagc tgcaactctc aaaggacacc tacgacgacg acttgacaa ttgctggca 840

caaattggcg atcagtacgc ggatctgttc cttgccgcta agaaccttc ggacgcaatc 900

ttgctgtccg atatcctgcg cgtgaacacc gaaataacca aagcgccgct tagcgctcg 960

atgattaagc ggtacgacga gcataccag gatctcacgc tgctcaaagc gctcgtgaga 1020

cagcaactgc ctgaaaagta caaggagatc ttcttcgacc agtccaagaa tgggtacgca 1080

gggtacatcg atggaggcgc tagccaggaa gatttctata agttcatcaa gccaatcctg 1140

gaaaagatgg acggaaccga agaactgctg gtcaagctga acaggaggga tctgctccgg 1200

aaacagagaa ctttgacaa cggatccatt cccaccaga tccatctggg tgagctgcac 1260

gccatcttgc ggcgccagga ggacttttac ccattcctca aggacaaccg ggaaaagatc 1320

gagaaaattc tgacgttccg catccgtat tacgtgggcc cactggcgcg cggcaattcg 1380

cgcttcgcgt ggatgactag aaaatcagag gaaaccatca ctcttgga ttctgaggaa 1440

gttgtggata agggagcttc ggcacaaagc ttcatcgaac gaatgaccaa cttcgacaag 1500

aatctcccaa acgagaaggt gcttcctaag cacagcctcc tttagaata cttcactgtc 1560

tacaacgaac tgactaaagt gaaatacgtt actgaaggaa tgaggaagcc ggcctttctg 1620

tccggagaac agaagaaagc aattgtgat ctgctgttca agaccaaccg caaggtgacc 1680

gtcaagcagc ttaaagagga ctactcaag aagatcgagt gtttcgactc agtggaatc 1740

agcggggtgg aggacagatt caacgcttcg ctgggaacct atcatgatct cctgaagatc 1800

atcaaggaca aggacttctt tgacaacgag gagaacgagg acatcctgga agatatcgtc 1860

ctgacctga cccttttcga ggatcgcgag atgatcgagg agaggcttaa gacctacgt 1920

catctcttcg acgataaggt catgaaacaa ctcaagcgcc gccggtacac tggttggggc 1980

cgctctccc gcaagctgat caacgttatt cgcgataaac agagcggtaa aactatcctg 2040

gatttctca aatcggatgg cttcgcta atcgtaactca tgcaattgat ccacgacgac 2100

agcctgacct ttaaggagga catcaaaaa gcacaagtgt ccggacagg agactcactc 2160

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attgaaatgg cccgagaaaa ccagactacc cagaagggcc agaaaaactc ccgcgaaagg 2340

atgaagcgga tcgaagaagg aatcaaggag ctgggcagcc agatcctgaa agagcaccgc 2400

gtggaaaaca cgagctgca gaacgagaag ctctacctgt actatttgca aaatggacgg 2460

gacatgtacg tggaccaaga gctggacatc aatcggttgt ctgattacga cgtggaccac 2520

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gacaagaaca gagggaagtc agataatgtg ccatcggagg aggtcgtgaa gaagatgaag 2640

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actaaatacg acgagaacga taagctcatc cggaagtga aggtgattac cctgaaaagc 2880

aaacttgtgt cggactttcg gaaggacttt cagttttaca aagtgagaga aatcaacaac 2940

taccatcacg cgcatgacgc atacctcaac gctgtggtcg gtaccgccct gatcaaaaag 3000

taccctaaac ttgaatcgga gtttgtgtac ggagactaca aggtctacga cgtgaggaag 3060

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aacatcatga actttttcaa gactgaaatt acgctggcca atggagaaat caggaagagg 3180

ccactgatcg aaactaacgg agaaacgggc gaaatcgtgt gggacaaggg cagggacttc 3240

gcaactgttc gcaaagtgt ctctatgccg caagtcaata ttgtgaagaa aaccgaagtg 3300

caaaccggcg gattttcaaa ggaatcgatc ctcccaaaga gaaatagcga caagtcatt 3360

gcacgcaaga aagactggga cccgaagaag tacggaggat tcgattcgcc gactgtcgca 3420

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aaagagctgc tggggattac catcatggaa cgatcctcgt tcgagaagaa cccgattgat 3540

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tactactgt tcgaactgga aaatggtcgg aagcgcatgc tggcttcggc cggagaactc 3660

caaaaaggaa atgagctggc cttgcctagc aagtacgtca acttcctcta tcttgcttcg 3720

cactacgaaa aactcaaagg gtcaccggaa gataacgaac agaagcagct ttcgtggag 3780

cagcacaagc attatctgga tgaaatcatc gaacaaatct ccgagtttc aaagcgcgtg 3840

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ccgatcagag aacaggccga gaacattatc cactgttca ccctgactaa cctgggagcc 3960

ccagccgcct tcaagtactt cgatactact atcgatcgca aaagatacac gtccaccaag 4020

gaagtcttgg acgcgaccct gatccaccaa agcatcactg gactctacga aactaggatc 4080

gatctgtcgc agctgggtgg cgatggcggg ggatctccga aaaagaagag aaaggtgtaa 4140

tga

4143

<210> 203

<211> 1379

<212> PRT

<213> Secuencia artificial

<220>

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

<400> 203

Met Asp Lys Lys Tyr Ser Ile Gly Leu Asp Ile Gly Thr Asn Ser Val

1 5 10 15

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

20 25 30

Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys Lys Asn Leu Ile

35 40 45

Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu

50 55 60

Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys

65 70 75 80

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

85 90 95

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

100 105 110

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

115 120 125

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

130 135 140

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

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 aauacaaggu cccgagcaag aaguucaagg uccugggaaa cacagacaga	120
cacagcauca agaagaaccu gaucggagca cugcuguucg acagcggaga aacagcagaa	180
gcaacaagac ugaagagaac agcaagaaga agauacacaa gaagaaagaa cagaaucugc	240
uaccugcagg aaaucuucag caacgaaaug gcaaaggucg acgacagcuu cuuccacaga	300
cuggaagaaa gcuuccuggu cgaagaagac aagaagcacg aaagacacc gaucuucgga	360
aaauaucugc 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
cgaucggag accaguacgc agaccuguuc cuggcagcaa agaaccugag cgacgcaauc	900

cugcugagcg acauccugag agucaacaca gaaaucacaa aggcaccgcu gagcgcaagc 960

augaucaaga gauacgacga acaccaccag gaccugacac ugcugaaggc acuggucaga 1020

cagcagcugc cggaagagua caaggaauc uucuucgacc agagcaagaa cggauacgca 1080

ggauacaucg acggaggagc aagccaggaa gaauucuaca aguucauaa gccgauccug 1140

gaaaagaugg acggaacaga agaacugcug gucaagcuga acagagaaga ccugcugaga 1200

aagcagagaa cauucgacaa cggaagcauc ccgcaccaga uccaccuggg agaacugcac 1260

gcaauccuga gaagacagga agacuucuac ccguuccuga aggacaacag agaaaagauc 1320

gaaaagaucc ugacauucag aaucccgua uacgucggac cgcuggcaag aggaaacagc 1380

agauucgcau ggauagacaag aaagagcgaa gaaacaauca caccugggaa cuucgaagaa 1440

gucgucgaca agggagcaag cgcacagagc uucaucgaaa gaaugacaaa cuucgacaag 1500

aaccugccga acgaaaaggu ccugccgaag cacagccugc uguacgaaua cuucacaguc 1560

uacaacgaac ugacaaaggu caaguacguc acagaaggaa ugagaaagcc ggcauuccug 1620

agcggagaac agaagaaggc aaucgucgac cugcuguuca agacaaacag aaaggucaca 1680

gucaagcagc ugaaggaaga cuacuuaag aagaucgaau gcuucgacag cgucgaaauc 1740

agcggagucg aagacagauu caacgcaagc cugggaacau accacgaccu gcugaagauc 1800
 aucaaggaca aggacuuccu ggacaacgaa gaaaacgaag acauccugga agaucguc 1860
 cugacacuga cacuguucga agacagagaa augaucgaag aaagacugaa gacauacga 1920
 caccuguucg acgacaaggu caugaagcag cugaagagaa gaagauacac aggaugggga 1980
 agacugagca gaaagcugau caacggaauc agagacaagc agagcggaaa gacaauccug 2040
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 gacauguacg ugcaccagga acuggacauc aacagacuga gcgacuacga cgucgaccac 2520
 aucguccgc agagcuuccu gaaggacgac agcaucgaca acaagguccu gacaagaagc 2580
 gacaagaaca gaggaagag cgacaacguc ccgagcgaag aagucgucaa gaagaugaag 2640

aacuacugga gacagcugcu gaacgcaaag cugaucacac agagaaaguu cgacaaccug 2700

acaaaggcag agagaggagg acugagcgaa cuggacaagg caggauucau caagagacag 2760

cuggucgaaa caagacagau cacaaagcac gucgcacaga uccuggacag cagaauaac 2820

acaaaguacg acgaaaacga caagcugauc agagaaguca aggucaucac acugaagagc 2880

aagcugguca gcgacuucag aaaggacuuc caguucuaca aggucaagaga aaucacaac 2940

uaccaccacg cacacgacgc auaccugaac gcagucgucg gaacagcacu gaucaagaag 3000

uaccgaagc uggaagcga auucgucuac ggagacuaca agguacuaga cgucagaaag 3060

augaucgcaa agagcgaaca ggaaucgga aaggcaacag caaaguacuu cuucuacagc 3120

aacauauga acuucuuaa gacagaaauc acacuggcaa acggagaaau cagaaagaga 3180

ccgcugaucg aaacaaacgg agaaacagga gaaucgucu gggacaaggg aagagacuuc 3240

gcaacaguca gaaagguccu gagcaugccg cagguaaca ucgucaagaa gacagaaguc 3300

cagacaggag gauucagcaa ggaaagcauc cugccgaaga gaaacagcga caagcugauc 3360

gcaagaaaga aggacuggga cccgaagaag uacggaggau ucgacagccc gacagucgca 3420

uacagcgucc uggucgucgc aaaggucgaa aagggaaga gcaagaagcu gaagagcguc 3480

aaggaacugc ugggaauacac aaucauggaa agaagcagcu ucgaaaagaa cccgaucgac 3540

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uacagccugu ucgaacugga aaacggaaga aagagaauugc uggcaagcgc aggagaacug 3660

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cacuacgaaa agcugaaggg aagcccggaa gacaacgaac agaagcagcu guucgucgaa 3780

cagcacaagc acuaccugga cgaaaauauc gaacagauca gcgaaauucag caagagaguc 3840

auccuggcag acgcaaaccu ggacaagguc cugagcgcau acaacaagca cagagacaag 3900

ccgaucagag aacaggcaga aaacauauc 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 aguacuaau cgggcuggau aucggaacua auuccugggg uugggcagug 60

aucacggaug aaaucaaagu gccguccaag aaguucaagg uccugggggaa caccgauaga 120

cacagcauca agaaaaaucu caucggagcc cugcuguuug acuccggcga aaccgcagaa 180

gcgacccggc ucaaacguac cgcgaggcga cgcuaacccc 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 ccucgccau 480

augaucaau uccgcggaca cuuccugauc gaaggcgau ugaaccuga uaacuccgac 540

guggauaagc uuuucauua acuggugcag accuacaacc aacuguucga agaaaacca 600

aucaaugcua gcggcgucga ugccaaggcc auccuguccg cccggcuguc gaagucgcgg 660

cgccucgaaa accugaucgc acagcugccg ggagagaaaa agaacggacu uuucggcaac 720

uugaucgcuc ucucacuggg acucacuccc aaauucaagu ccaauuuuga ccuggccgag 780

gagcggaagc ugcaacucuc aaaggacacc uacgacgacg acuuggacaa uuugcuggca	840
caaauggcg aucaguacgc ggaucuguuc cuugccgcu agaaccuuuc ggacgcauc	900
uugcuguccg auauccugcg cgugaacacc gaaauaacca aagcgccgcu uagcgccucg	960
augauuaagc gguacgacga gcauccagc gaucucacgc ugcuaaaagc gcucgugaga	1020
cagcaacugc cugaaaagua caaggagauc uucuucgacc aguccaagaa uggguacgca	1080
ggguacaucg auggagcgcg uagccaggaa gaguucuaua aguucauaa gccauuccug	1140
gaaaagaugg acggaaccga agaacugcug gucaagcuga acaggaggga ucugcuccgg	1200
aaacagagaa ccuuugacaa cggauccauu cccaccaga uccaucuggg ugagcugcac	1260
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cgcuuvcgu ggaugacuag aaaucagag gaaaccauca cuccuuggaa uuucgaggaa	1440
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aaucuccaa acgagaaggu gcuuccuag cacagccucc uuucgaaua cuucacuguc	1560
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uccggagaac agaagaaagc aaugucgau cugcuguuca agaccaaccg caaggugacc 1680

gucaagcagc uuaaagagga cuacucaag aagaucgagu guuucgacuc aguggaaauc 1740

agcggggugg aggacagauu caacgcuucg cugggaaccu aucaugaucu ccugaagauc 1800

aucaaggaca aggacuuccu ugacaacgag gagaacgagg acauccugga agauaucguc 1860

cugaccuuga cccuuuucga ggauccgagc augaucgagg agaggcuuaa gaccuacgc 1920

caucucuucg acgauaaggu caugaaaca cucaagcgcc gccgguacac ugguuggggc 1980

cgccucuccc gcaagcugau caacgguaau cgcgauaaac agagcgguaa aacuauccug 2040

gauuuccuca aaucggauug cuucgcuaau cguaacuuca ugcaauugau ccacgacgac 2100

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guggaaaaca cgcagcugca gaacgagaag cucuaccugu acuaauugca aaauggacgg 2460

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gaaguucugg acgcgacccu gauccacaa agcaucacug gacucuacga aacuaggau 4080

gaucugucgc agcugggugg cgauggcggu ggauuccga 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)

<400> 207

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cacagcauca agaagaaccu gaucggagca cugcuguucg acagcggaga aacagcagaa 180

gcaacaagac ugaagagaac agcaagaaga agauacacaa gaagaaagaa cagaaucugc	240
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cuggaagaaa gcuuccuggu cgaagaagac aagaagcacg aaagacaccc gaucuucgga	360
aacaucgucg acgaagucgc auaccacgaa aaguacccga caaucuacca ccugagaaag	420
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gucgacaagc uguucaucca gcugguccag acauacaacc agcuguucga agaaaacccg	600
aucaacgcaa gcggagucga cgcaaaggca auccugagcg caagacugag caagagcaga	660
agacuggaaa accugaucgc acagcugccg ggagaaaaga agaacggacu guucggaaac	720
cugaucgcac ugagccuggg acugacaccg aacuucaaga gcaacuucga ccuggcagaa	780
gacgcaaagc ugcagcugag caaggacaca uacgacgacg accuggacaa ccugcuggca	840
cagaucggag accaguacgc agaccuguuc cuggcagcaa agaaccugag cgacgcauc	900
cugcugagcg acauccugag agucaacaca gaaucacaa aggcaccgcu gagcgcaagc	960
augaucaaga gauacgacga acaccaccag gaccugacac ugcugaaggc acuggucaga	1020
cagcagcugc cggaaaagua caaggaaauc uucuucgacc agagcaagaa cggauacgca	1080

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 aucaaggaca aggacuuccu ggacaacgaa gaaaacgaag acauccugga agacaucguc 1860
 cugacacuga cacuguucga agacagagaa augaucgaag aaagacugaa gacauacgca 1920

caccuguucg acgacaaggu caugaagcag cugaagagaa gaagauacac aggaugggga 1980

agacugagca gaaagcugau caacggaauc agagacaagc agagcggaaa gacaauccug 2040

gacuuccuga agagcgacgg auucgcaaac agaaacuua ugcagcugau ccacgacgac 2100

agccugacau ucaaggaaga cauccagaag gcacagguca gcggacaggg agacagccug 2160

cacgaacaca ucgcaaaccu ggcaaggagc ccggcaauca agaagggaau ccugcagaca 2220

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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> 208

<211> 1379

<212> PRT

<213> Secuencia artificial

<220>

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

<400> 208

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

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25

30

Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys Lys Asn Leu Ile

35

40

45

Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu

50

55

60

Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys

65

70

75

80

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

85

90

95

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

100

105

110

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

115

120

125

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

130

135

140

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

145

150

155

160

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

165

170

175

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

180

185

190

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

195

200

205

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

210

215

220

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

225

230

235

240

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

245

250

255

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

260

265

270

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

275

280

285

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

290

295

300

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

305

310

315

320

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

325

330

335

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

340

345

350

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

355 360 365

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

370 375 380

Gly Thr Glu Glu Leu Leu Val Lys Leu Asn Arg Glu Asp Leu Leu Arg

385 390 395 400

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

405 410 415

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

420 425 430

Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile

435 440 445

Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp

450 455 460

Met Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu

465 470 475 480

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

485

490

495

Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys Val Leu Pro Lys His Ser

500

505

510

Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu Leu Thr Lys Val Lys

515

520

525

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

530

535

540

Lys Lys Ala Ile Val Asp Leu Leu Phe Lys Thr Asn Arg Lys Val Thr

545

550

555

560

Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp

565

570

575

Ser Val Glu Ile Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu Gly

580

585

590

Thr Tyr His Asp Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp

595 600 605

Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile Val Leu Thr Leu Thr

610 615 620

Leu Phe Glu Asp Arg Glu Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala

625 630 635 640

His Leu Phe Asp Asp Lys Val Met Lys Gln Leu Lys Arg Arg Arg Tyr

645 650 655

Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp

660 665 670

Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe

675 680 685

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

690 695 700

Lys Glu Asp Ile Gln Lys Ala Gln Val Ser Gly Gln Gly Asp Ser Leu

705 710 715 720

His Glu His Ile Ala Asn Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly

725 730 735

Ile Leu Gln Thr Val Lys Val Val Asp Glu Leu Val Lys Val Met Gly

740 745 750

Arg His Lys Pro Glu Asn Ile Val Ile Glu Met Ala Arg Glu Asn Gln

755 760 765

Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu Arg Met Lys Arg Ile

770 775 780

Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile Leu Lys Glu His Pro

785 790 795 800

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

805 810 815

Gln Asn Gly Arg Asp Met Tyr Val Asp Gln Glu Leu Asp Ile Asn Arg

820 825 830

Leu Ser Asp Tyr Asp Val Asp Ala Ile Val Pro Gln Ser Phe Leu Lys

835 840 845

Asp Asp Ser Ile Asp Asn Lys Val Leu Thr Arg Ser Asp Lys Asn Arg

850 855 860

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

865 870 875 880

Asn Tyr Trp Arg Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys

885 890 895

Phe Asp Asn Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp

900 905 910

Lys Ala Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr

915 920 925

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

930 935 940

Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys Ser

945 950 955 960

Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys Val Arg

965 970 975

Glu Ile Asn Asn Tyr His His Ala His Asp Ala Tyr Leu Asn Ala Val

980 985 990

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

995 1000 1005

Val Tyr Gly Asp Tyr Lys Val Tyr Asp Val Arg Lys Met Ile Ala

1010 1015 1020

Lys Ser Glu Gln Glu Ile Gly Lys Ala Thr Ala Lys Tyr Phe Phe

1025 1030 1035

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

1040 1045 1050

Asn Gly Glu Ile Arg Lys Arg Pro Leu Ile Glu Thr Asn Gly Glu

1055 1060 1065

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

1070 1075 1080

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

1085 1090 1095

Glu Val Gln Thr Gly Gly Phe Ser Lys Glu Ser Ile Leu Pro Lys

1100 1105 1110

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

1115 1120 1125

Lys Lys Tyr Gly Gly Phe Asp Ser Pro Thr Val Ala Tyr Ser Val

1130 1135 1140

Leu Val Val Ala Lys Val Glu Lys Gly Lys Ser Lys Lys Leu Lys

1145 1150 1155

Ser Val Lys Glu Leu Leu Gly Ile Thr Ile Met Glu Arg Ser Ser

1160 1165 1170

Phe Glu Lys Asn Pro Ile Asp Phe Leu Glu Ala Lys Gly Tyr Lys

1175 1180 1185

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

1190 1195 1200

Phe Glu Leu Glu Asn Gly Arg Lys Arg Met Leu Ala Ser Ala Gly

1205 1210 1215

Glu Leu Gln Lys Gly Asn Glu Leu Ala Leu Pro Ser Lys Tyr Val

1220 1225 1230

Asn Phe Leu Tyr Leu Ala Ser His Tyr Glu Lys Leu Lys Gly Ser

1235 1240 1245

Pro Glu Asp Asn Glu Gln Lys Gln Leu Phe Val Glu Gln His Lys

1250 1255 1260

His Tyr Leu Asp Glu Ile Ile Glu Gln Ile Ser Glu Phe Ser Lys

1265 1270 1275

Arg Val Ile Leu Ala Asp Ala Asn Leu Asp Lys Val Leu Ser Ala

1280 1285 1290

Tyr Asn Lys His Arg Asp Lys Pro Ile Arg Glu Gln Ala Glu Asn

1295 1300 1305

Ile Ile His Leu Phe Thr Leu Thr Asn Leu Gly Ala Pro Ala Ala

1310 1315 1320

Phe Lys Tyr Phe Asp Thr Thr Ile Asp Arg Lys Arg Tyr Thr Ser

1325 1330 1335

Thr Lys Glu Val Leu Asp Ala Thr Leu Ile His Gln Ser Ile Thr

1340 1345 1350

Gly Leu Tyr Glu Thr Arg Ile Asp Leu Ser Gln Leu Gly Gly Asp

1355 1360 1365

Gly Gly Gly Ser Pro Lys Lys Lys Arg Lys Val

1370 1375

<210> 209

<211> 4140

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 209

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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

aacaucgucg acgaagucgc auaccacgaa aaguaccgga caaucuacca ccugagaaag 420

aagcuggucg acagcacaga caaggcagac cugagacuga ucuaccuggc acuggcacac 480

augaucaagu ucagaggaca cuuccugauc gaaggagacc ugaaccgga caacagcgac 540

gucgacaagc uguucaucca gcugguccag acauacaacc agcuguucga agaaaacccg	600
aucaacgcaa gcggagucga cgcaaaggca auccugagcg caagacugag caagagcaga	660
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cugcugagcg acauccugag agucaacaca gaaucacaa aggcaccgcu gagcgcaagc	960
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uacaacgaac ugacaaaggu caaguacguc acagaaggaa ugagaaagcc ggcauuccug 1620

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gucaagcagc ugaaggaaga cuacuucaag aagaucgaau gcuucgacag cgucgaaauc 1740

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aucaaggaca aggacuuccu ggacaacgaa gaaaacgaag acauccugga agacaucguc 1860

cugacacuga cacuguucga agacagagaa augaucgaag aaagacugaa gacauacgca 1920

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agacugagca gaaagcugau caacggaauc agagacaagc agagcggaaa gacaauccug 2040

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<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

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acaagacuga agagaacagc aagaagaaga uacacaagaa gaaagaacag aaucugcuac 240

cugcaggaaa ucuucagcaa cgaaauggca aaggucgacg acagcuucuu ccacagacug 300

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gcagcauua aguacuucga cacaacauc gacagaaaga gauacacaag cacaagga 4020

guccuggacg caacacugau ccaccagagc aucacaggac uguacgaaac aagaaucgac 4080

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<210> 211

<211> 4134

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 211

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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 ggagaccug 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 gcugagaaaag	1200

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acacugacac uguucgaaga cagagaaaug aucgaagaaa gacugaagac auacgcacac 1920

cuguucgacg acaaggucua gaagcagcug aagagaagaa gauacacagg auggggaaga 1980

cugagcagaa agcugaucaa cggaaucaga gacaagcaga gcggaaagac aauccuggac 2040

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<210> 212

<211> 4134

<212> ARN

<213> Secuencia artificial

<220>

<223> Sintético: secuencia de codificación desnuda de dCas9

<400> 212

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agcaucaaga agaaccugau cggagcacug cuguucgaca gcggagaaac agcagaagca 180

acaagacuga agagaacagc aagaagaaga uacacaagaa gaaagaacag aaucugcuac 240

cugcaggaaa ucuucagcaa cgaaauggca aaggucgacg acagcuucuu ccacagacug	300
gaagaaagcu uccuggucga agaagacaag aagcacgaaa gacacccgau cuucggaaac	360
aucgucgacg aagucgcaua ccacgaaaag uacccgacaa ucuaccaccu gagaaagaag	420
cuggucgaca gcacagacaa ggacagaccug agacugaucu accuggcacu ggcacacaug	480
aucaaguuca gaggacacuu ccugaucgaa ggagaccuga acccggacaa cagcgacguc	540
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aacgcaagcg gagucgacgc aaaggcaauc cugagcgcaa gacugagcaa gagcagaaga	660
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aucgcacuga gccugggacu gacaccgaac uucaagagca acuucgaccu ggcagaagac	780
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cugagcgaca uccugagagu caacacagaa aucacaaagg caccgcugag cgcaagcaug	960
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<211> 1368

<212> PRT

<213> Secuencia artificial

<220>

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

<400> 213

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20

25

30

Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys Lys Asn Leu Ile

35

40

45

Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu

50

55

60

Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys

65

70

75

80

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

85

90

95

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

100

105

110

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

115

120

125

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

130

135

140

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

145

150

155

160

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

165

170

175

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

180

185

190

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

195

200

205

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

210

215

220

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

225

230

235

240

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

245 250 255

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

260 265 270

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

275 280 285

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

290 295 300

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

305 310 315 320

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

325 330 335

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

340 345 350

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

355 360 365

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

370

375

380

Gly Thr Glu Glu Leu Leu Val Lys Leu Asn Arg Glu Asp Leu Leu Arg

385

390

395

400

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

405

410

415

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

420

425

430

Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile

435

440

445

Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp

450

455

460

Met Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu

465

470

475

480

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

485

490

495

Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys Val Leu Pro Lys His Ser

500

505

510

Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu Leu Thr Lys Val Lys

515

520

525

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

530

535

540

Lys Lys Ala Ile Val Asp Leu Leu Phe Lys Thr Asn Arg Lys Val Thr

545

550

555

560

Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp

565

570

575

Ser Val Glu Ile Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu Gly

580

585

590

Thr Tyr His Asp Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp

595 600 605

Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile Val Leu Thr Leu Thr

610 615 620

Leu Phe Glu Asp Arg Glu Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala

625 630 635 640

His Leu Phe Asp Asp Lys Val Met Lys Gln Leu Lys Arg Arg Arg Tyr

645 650 655

Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp

660 665 670

Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe

675 680 685

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

690 695 700

Lys Glu Asp Ile Gln Lys Ala Gln Val Ser Gly Gln Gly Asp Ser Leu

705 710 715 720

His Glu His Ile Ala Asn Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly

725 730 735

Ile Leu Gln Thr Val Lys Val Val Asp Glu Leu Val Lys Val Met Gly

740 745 750

Arg His Lys Pro Glu Asn Ile Val Ile Glu Met Ala Arg Glu Asn Gln

755 760 765

Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu Arg Met Lys Arg Ile

770 775 780

Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile Leu Lys Glu His Pro

785 790 795 800

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

805 810 815

Gln Asn Gly Arg Asp Met Tyr Val Asp Gln Glu Leu Asp Ile Asn Arg

820 825 830

Leu Ser Asp Tyr Asp Val Asp His Ile Val Pro Gln Ser Phe Leu Lys

835 840 845

Asp Asp Ser Ile Asp Asn Lys Val Leu Thr Arg Ser Asp Lys Asn Arg

850 855 860

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

865 870 875 880

Asn Tyr Trp Arg Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys

885 890 895

Phe Asp Asn Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp

900 905 910

Lys Ala Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr

915 920 925

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

930 935 940

Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys Ser

945 950 955 960

Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys Val Arg

965 970 975

Glu Ile Asn Asn Tyr His His Ala His Asp Ala Tyr Leu Asn Ala Val

980 985 990

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

995 1000 1005

Val Tyr Gly Asp Tyr Lys Val Tyr Asp Val Arg Lys Met Ile Ala

1010 1015 1020

Lys Ser Glu Gln Glu Ile Gly Lys Ala Thr Ala Lys Tyr Phe Phe

1025 1030 1035

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

1040 1045 1050

Asn Gly Glu Ile Arg Lys Arg Pro Leu Ile Glu Thr Asn Gly Glu

1055 1060 1065

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

1070 1075 1080

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

1085 1090 1095

Glu Val Gln Thr Gly Gly Phe Ser Lys Glu Ser Ile Leu Pro Lys

1100 1105 1110

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

1115 1120 1125

Lys Lys Tyr Gly Gly Phe Asp Ser Pro Thr Val Ala Tyr Ser Val

1130 1135 1140

Leu Val Val Ala Lys Val Glu Lys Gly Lys Ser Lys Lys Leu Lys

1145 1150 1155

Ser Val Lys Glu Leu Leu Gly Ile Thr Ile Met Glu Arg Ser Ser

1160 1165 1170

Phe Glu Lys Asn Pro Ile Asp Phe Leu Glu Ala Lys Gly Tyr Lys

1175 1180 1185

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

1190 1195 1200

Phe Glu Leu Glu Asn Gly Arg Lys Arg Met Leu Ala Ser Ala Gly

1205 1210 1215

Glu Leu Gln Lys Gly Asn Glu Leu Ala Leu Pro Ser Lys Tyr Val

1220 1225 1230

Asn Phe Leu Tyr Leu Ala Ser His Tyr Glu Lys Leu Lys Gly Ser

1235 1240 1245

Pro Glu Asp Asn Glu Gln Lys Gln Leu Phe Val Glu Gln His Lys

1250 1255 1260

His Tyr Leu Asp Glu Ile Ile Glu Gln Ile Ser Glu Phe Ser Lys

1265 1270 1275

Arg Val Ile Leu Ala Asp Ala Asn Leu Asp Lys Val Leu Ser Ala

1280 1285 1290

Tyr Asn Lys His Arg Asp Lys Pro Ile Arg Glu Gln Ala Glu Asn

1295 1300 1305

Ile Ile His Leu Phe Thr Leu Thr Asn Leu Gly Ala Pro Ala Ala

1310 1315 1320

Phe Lys Tyr Phe Asp Thr Thr Ile Asp Arg Lys Arg Tyr Thr Ser

1325 1330 1335

Thr Lys Glu Val Leu Asp Ala Thr Leu Ile His Gln Ser Ile Thr

1340 1345 1350

Gly Leu Tyr Glu Thr Arg Ile Asp Leu Ser Gln Leu Gly Gly Asp

1355 1360 1365

<210> 214

<211> 4107

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 214

auggacaaga aguacagcau cggacuggac aucggaacaa acagcgucgg augggcaguc 60

aucacagacg aaaucaaggu cccgagcaag aaguucaagg uccugggaaa cacagacaga 120

cacagcauca agaagaaccu gaucggagca cugcuguucg acagcggaga aacagcagaa 180

gcaacaagac ugaagagaac agcaagaaga agauacacaa gaagaaagaa cagaaucugc 240

uaccugcagg aaaucuucag caacgaaaug gcaaaggucg acgacagcuu cuuccacaga 300

cuggaagaaa gcuuccuggu cgaagaagac aagaagcacg aaagacaccc gaucuucgga 360

aauaucgucg acgaagucgc auaccacgaa aaguaccgga caaucuacca ccugagaaaag 420

aagcuggucg acagcacaga caaggcagac cugagacuga ucuaccuggc acuggcacac 480

augaucaagu ucagaggaca cuuccugauc gaaggagacc ugaaccgga caacagcgac 540

gucgacaagc uguucaucca gcugguccag acauacaacc agcuguucga agaaaacccg 600

aucaacgcaa gcggagucga cgcaaaggca auccugagcg caagacugag caagagcaga 660

agacuggaaa accugaucgc acagcugccg ggagaaaaga agaacggacu guucggaaac	720
cugaucgcac ugagccuggg acugacaccg aacuuaaga gcaacuucga ccuggcagaa	780
gagcaaagc ugcagcugag caaggacaca uacgacgacg accuggacaa ccugcuggca	840
cagaucggag accaguacgc agaccuguuc cuggcagcaa agaaccugag cgacgcauc	900
cugcugagcg acauccugag agucaacaca gaaucacaa aggcaccgcu gagcgcaagc	960
augaucaaga gauacgacga acaccaccg gaccugacac ugcugaaggc acuggucaga	1020
cagcagcugc cggaaaagua caaggaaauc uucuucgacc agagcaagaa cggauacgca	1080
ggauacaucg acggaggagc aagccaggaa gaauucuaca aguucauca gccgauccug	1140
gaaaagaugg acggaacaga agaacugcug gucaagcuga acagagaaga ccugcugaga	1200
aagcagagaa cauucgacaa cggaagcauc ccgcaccaga uccaccuggg agaacugcac	1260
gcaauccuga gaagacagga agacuucuac ccguuccuga aggacaacag agaaaagauc	1320
gaaaagaucc ugacauucag aaucccgua uacgucggac cgcuggcaag aggaaacagc	1380
agauucgau ggauagacaag aaagagcgaa gaaacaauc caccugggaa cuucgaagaa	1440
gucgucgaca agggagcaag cgcacagagc uucaucgaaa gaaugacaaa cuucgacaag	1500
aaccugccga acgaaaaggu ccugccgaag cacagccugc uguacgaaua cuucacaguc	1560

uacaacgaac ugacaaaggu caaguacguc acagaaggaa ugagaaagcc ggcauuccug 1620
 agcggagaac agaagaaggc aaucgucgac cugcuguuca agacaaacag aaaggucaca 1680
 gucaagcagc ugaaggaaga cuacuucaag aagaucgaau gcuucgacag cgucgaaauc 1740
 agcggagucg aagacagauu caacgcaagc cugggaacau accacgaccu gcugaagauc 1800
 aucaaggaca aggacuuccu ggacaacgaa gaaaacgaag acauccugga agaucguc 1860
 cugacacuga cacuguucga agacagagaa augaucgaag aaagacugaa gacauacgca 1920
 caccuguucg acgacaaggu caugaagcag cugaagagaa gaagauacac aggaugggga 1980
 agacugagca gaaagcugau caacggaauc agagacaagc agagcggaaa gacaauccug 2040
 gacuuccuga agagcgacgg auucgcaaac agaaacuuca ugcagcugau ccacgacgac 2100
 agccugacau ucaaggaaga cauccagaag gcacagguca gcggacaggg agacagccug 2160
 cacgaacaca ucgcaaaccu ggaggaagc ccggcaauca agaagggaau ccugcagaca 2220
 gucaaggucg ugcacgaacu ggucaagguc augggaagac acaagccgga aaacaucguc 2280
 aucgaaugg caagagaaaa ccagacaaca cagaagggac agaagaacag cagagaaaga 2340
 augaagagaa ucgaagaagg aaucaggaa cugggaagcc agauccugaa ggaacaccg 2400

gucgaaaaca cacagcugca gaacgaaaag cuguaccugu acuaccugca gaacggaaga 2460

gacauguacg ucgaccagga acuggacauc aacagacuga gcgacuacga cgucgaccac 2520

aucguccgc agagcuuccu gaaggacgac agcaucgaca acaagguccu gacaagaagc 2580

gacaagaaca gaggaaagag cgacaacguc ccgagcgaag aagucgucaa gaagaugaag 2640

aacuacugga gacagcugcu gaacgcaaag cugaucacac agagaaaguu cgacaaccug 2700

acaaaggcag agagaggagg acugagcgaa cuggacaagg caggauucau caagagacag 2760

cuggucgaaa caagacagau cacaagcac gucgcacaga uccuggacag cagaaugaac 2820

acaaaguacg acgaaaacga caagcugauc agagaaguca aggucaucac acugaagagc 2880

aagcugguca gcgacuucag aaaggacuuc caguucuaca agguagaga aaucacaac 2940

uaccaccag cacacgacgc auaccugaac gcagucgucg gaacagcacu gaucaagaag 3000

uaccgaagc uggaaagcga auucgucuac ggagacuaca agguacuaga cgucagaaag 3060

augaucgaa agagcgaaca ggaaucgga aaggcaacag caaguacuu cuucuacagc 3120

aacauauga acuucucaa gacagaaauc acacuggcaa acggagaaau cagaaagaga 3180

ccgcugaucg aaacaaacgg agaaacagga gaaucgucu gggacaaggg aagagacuuc 3240

gcaacaguca gaaagguccu gagcaugccg cagguaaca ucgucaagaa gacagaaguc 3300

cagacaggag gauucagcaa ggaaagcauc cugccgaaga gaaacagcga caagcugauc	3360
gcaagaaaga aggacuggga cccgaagaag uacggaggau ucgacagccc gacagucgca	3420
uacagcgucc uggucgucgc aaaggucgaa aagggaaga gcaagaagcu gaagagcguc	3480
aaggaacugc ugggaaucaac aaucauggaa agaagcagcu ucgaaaagaa ccggaucgac	3540
uuccuggaag caaagggaau caaggaaguc aagaaggacc ugaucaucaa gcugccgaag	3600
uacagccugu ucgaacugga aaacggaaga aagagaaucg uggcaagcgc aggagaacug	3660
cagaagggaac acgaacuggc acugccgagc aaguacguca acuuccugua ccuggcaagc	3720
cacuacgaaa agcugaaggg aagcccggaa gacaacgaac agaagcagcu guucgucgaa	3780
cagcacaagc acuaccugga cgaaaaucauc gaacagauca gcgaaauucag caagagaguc	3840
auccuggcag acgcaaaccu ggacaagguc cugagcgcau acaacaagca cagagacaag	3900
ccgaucagag aacaggcaga aaacaucauc caccuguuca cacugacaaa ccugggagca	3960
ccggcagcau ucaaguacuu cgacacaaca aucgacagaa agagauacac aagcacaag	4020
gaaguccugg acgcaacacu gauccaccag agcaucacag gacuguacga aacaagauc	4080
gaccugagcc agcugggagg agacuag	4107

<210> 215

<211> 4101

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 215

gacaagaagu acagcaucgg acuggacauc ggaacaaaca gcgucggaug ggcagucauc 60

acagacgaau acaaggucgg 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 ggcaagaagac	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
ucaucgacg 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 cgaaucagc 1740
 ggagucgaag acagauuca cgcaagccug ggaacauacc acgaccugcu gaagaucauc 1800
 aaggacaagg acuuccugga caacgaagaa aacgaagaca uccuggaaga caucguccug 1860
 acacugacac uguucgaaga cagagaaaug aucgaagaaa gacugaagac auacgcacac 1920
 cuguucgacg acaaggucuu gaagcagcug aagagaagaa gauacacagg auggggaaga 1980
 cugagcagaa agcugaucaa cggaaucaga gacaagcaga gcggaagac aauccuggac 2040
 uuccugaaga gcgacggauu cgcaaacaga aacuucugc agcugaucca cgacgacagc 2100
 cugacauuca aggaagacau ccagaaggca caggucagcg gacagggaga cagccugcac 2160
 gaacacaucg caaaccuggc aggaagcccg gcaaucaaga agggaauccu gcagacaguc 2220
 aaggucgucg acgaacuggu caagguaug ggaagacaca agccgaaaa caucgucauc 2280

gaaauaggcaa gagaaaacca gacaacacag aaggacaga agaacagcag agaaagaaug 2340
 aagagaauug aagaaggaau caaggaacug ggaagccaga uccugaagga acacccgguc 2400
 gaaaacacac agcugcagaa cgaaaagcug uaccuguacu accugcagaa cggaagagac 2460
 auguacgucg accaggaacu ggacaucaac agacugagcg acuacgacgu cgaccacauc 2520
 guccgcaga gcuuccugaa ggacgacagc aucgacaaca agguccugac aagaagcgac 2580
 aagaacagag gaaagagcga caacgucccg agcgaagaag ucucaagaa gaugaagaac 2640
 uacuggagac agcugcugaa cgcaaagcug aucacacaga gaaaguucga caaccugaca 2700
 aaggcagaga gaggaggacu gagcgaacug gacaaggcag gauucauca gagacagcug 2760
 gucgaaacaa gacagaucaac aaagcacguc gcacagaucc uggacagcag aaugaacaca 2820
 aaguacgacg aaaacgacaa gcugaucaga gaagucaagg ucaucacacu gaagagcaag 2880
 cuggucagcg acuucagaaa ggacuuccag uucuacaagg ucagagaaa caacaacuac 2940
 caccacgac acgacgcaua ccugaacgca gucgucggaa cagcacugau caagaaguac 3000
 ccgaagcugg aaagcgaaau cgucuacgga gacuacaagg ucuacgacgu cagaaagaug 3060
 aucgcaaaga gcgaacagga aaucggaaag gcaacagcaa aguacuucuu cuacagcaac 3120

aucaugaacu ucuucaagac agaaucaca cuggcaaacg gagaaucag aaagagaccg 3180

cugaucgaaa caaacggaga aacaggagaa aucgucuggg acaagggaag agacuucgca 3240

acagucagaa agguccugag caugccgcag gucaaucug ucaagaagac agaaguccag 3300

acaggaggau ucagcaagga aagcauccug ccgaagagaa acagcgacaa gcugaucgca 3360

agaaagaagg acugggaccc gaagaaguac ggaggauucg acagcccgac agucgcauac 3420

agcguccugg ucgucgcaaa ggucgaaaag ggaaagagca agaagcugaa gagcgucaag 3480

gaacugcugg gaucacaaau cauggaaaga agcagcuucg aaaagaaccc gaucgacuuc 3540

cuggaagcaa agggauacaa ggaagucaag aaggaccuga ucaucaagcu gccgaaguac 3600

agccguuucg aacuggaaaa cggaagaaag agaaucugg caagcgagg agaacugcag 3660

aagggaacg aacuggcacu gccgagcaag uacgucaacu uccuguaccu ggcaagccac 3720

uacgaaaagc ugaagggaag cccggaagac aacgaacaga agcagcuguu cgucgaacag 3780

cacaagcacu accuggacga aaucaucgaa cagaucagcg aaucagcaa gagagucauc 3840

cuggcagacg caaaccugga caagguccug agcgcauaca acaagcacag agacaagccg 3900

aucagagaac aggcagaaaa caucauccac cuguucacac ugacaaaccu gggagcaccg 3960

gcagcauua aguacuucga cacaacauc gacagaaaga gauacacaag cacaaggaa 4020

guccuggacg caacacugau ccaccagagc aucacaggac uguacgaaac aagaaucgac 4080

cugagccagc ugaggaggaga c 4101

<210> 216

<211> 1368

<212> PRT

<213> Secuencia artificial

<220>

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

<400> 216

Met Asp Lys Lys Tyr Ser Ile Gly Leu Ala Ile Gly Thr Asn Ser Val

1 5 10 15

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

20 25 30

Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys Lys Asn Leu Ile

35 40 45

Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu

50 55 60

Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys

65 70 75 80

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

85 90 95

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

100 105 110

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

115 120 125

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

130 135 140

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

145 150 155 160

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

165 170 175

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

180

185

190

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

195

200

205

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

210

215

220

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

225

230

235

240

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

245

250

255

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

260

265

270

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

275

280

285

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

290

295

300

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

305

310

315

320

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

325

330

335

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

340

345

350

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

355

360

365

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

370

375

380

Gly Thr Glu Glu Leu Leu Val Lys Leu Asn Arg Glu Asp Leu Leu Arg

385

390

395

400

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

405

410

415

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

420

425

430

Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile

435

440

445

Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp

450

455

460

Met Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu

465

470

475

480

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

485

490

495

Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys Val Leu Pro Lys His Ser

500

505

510

Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu Leu Thr Lys Val Lys

515 520 525

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

530 535 540

Lys Lys Ala Ile Val Asp Leu Leu Phe Lys Thr Asn Arg Lys Val Thr

545 550 555 560

Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp

565 570 575

Ser Val Glu Ile Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu Gly

580 585 590

Thr Tyr His Asp Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp

595 600 605

Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile Val Leu Thr Leu Thr

610 615 620

Leu Phe Glu Asp Arg Glu Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala

625 630 635 640

His Leu Phe Asp Asp Lys Val Met Lys Gln Leu Lys Arg Arg Arg Tyr

645

650

655

Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp

660

665

670

Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe

675

680

685

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

690

695

700

Lys Glu Asp Ile Gln Lys Ala Gln Val Ser Gly Gln Gly Asp Ser Leu

705

710

715

720

His Glu His Ile Ala Asn Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly

725

730

735

Ile Leu Gln Thr Val Lys Val Val Asp Glu Leu Val Lys Val Met Gly

740

745

750

Arg His Lys Pro Glu Asn Ile Val Ile Glu Met Ala Arg Glu Asn Gln

755 760 765

Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu Arg Met Lys Arg Ile

770 775 780

Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile Leu Lys Glu His Pro

785 790 795 800

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

805 810 815

Gln Asn Gly Arg Asp Met Tyr Val Asp Gln Glu Leu Asp Ile Asn Arg

820 825 830

Leu Ser Asp Tyr Asp Val Asp His Ile Val Pro Gln Ser Phe Leu Lys

835 840 845

Asp Asp Ser Ile Asp Asn Lys Val Leu Thr Arg Ser Asp Lys Asn Arg

850 855 860

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

865 870 875 880

Asn Tyr Trp Arg Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys

885 890 895

Phe Asp Asn Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp

900 905 910

Lys Ala Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr

915 920 925

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

930 935 940

Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys Ser

945 950 955 960

Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys Val Arg

965 970 975

Glu Ile Asn Asn Tyr His His Ala His Asp Ala Tyr Leu Asn Ala Val

980 985 990

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

995 1000 1005

Val Tyr Gly Asp Tyr Lys Val Tyr Asp Val Arg Lys Met Ile Ala

1010 1015 1020

Lys Ser Glu Gln Glu Ile Gly Lys Ala Thr Ala Lys Tyr Phe Phe

1025 1030 1035

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

1040 1045 1050

Asn Gly Glu Ile Arg Lys Arg Pro Leu Ile Glu Thr Asn Gly Glu

1055 1060 1065

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

1070 1075 1080

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

1085 1090 1095

Glu Val Gln Thr Gly Gly Phe Ser Lys Glu Ser Ile Leu Pro Lys

1100 1105 1110

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

1115 1120 1125

Lys Lys Tyr Gly Gly Phe Asp Ser Pro Thr Val Ala Tyr Ser Val

1130 1135 1140

Leu Val Val Ala Lys Val Glu Lys Gly Lys Ser Lys Lys Leu Lys

1145 1150 1155

Ser Val Lys Glu Leu Leu Gly Ile Thr Ile Met Glu Arg Ser Ser

1160 1165 1170

Phe Glu Lys Asn Pro Ile Asp Phe Leu Glu Ala Lys Gly Tyr Lys

1175 1180 1185

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

1190 1195 1200

Phe Glu Leu Glu Asn Gly Arg Lys Arg Met Leu Ala Ser Ala Gly

1205 1210 1215

Glu Leu Gln Lys Gly Asn Glu Leu Ala Leu Pro Ser Lys Tyr Val

1220 1225 1230

Asn Phe Leu Tyr Leu Ala Ser His Tyr Glu Lys Leu Lys Gly Ser

1235 1240 1245

Pro Glu Asp Asn Glu Gln Lys Gln Leu Phe Val Glu Gln His Lys

1250 1255 1260

His Tyr Leu Asp Glu Ile Ile Glu Gln Ile Ser Glu Phe Ser Lys

1265 1270 1275

Arg Val Ile Leu Ala Asp Ala Asn Leu Asp Lys Val Leu Ser Ala

1280 1285 1290

Tyr Asn Lys His Arg Asp Lys Pro Ile Arg Glu Gln Ala Glu Asn

1295 1300 1305

Ile Ile His Leu Phe Thr Leu Thr Asn Leu Gly Ala Pro Ala Ala

1310 1315 1320

Phe Lys Tyr Phe Asp Thr Thr Ile Asp Arg Lys Arg Tyr Thr Ser

1325 1330 1335

Thr Lys Glu Val Leu Asp Ala Thr Leu Ile His Gln Ser Ile Thr

1340 1345 1350

Gly Leu Tyr Glu Thr Arg Ile Asp Leu Ser Gln Leu Gly Gly Asp

1355 1360 1365

<210> 217

<211> 4107

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 217

auggacaaga aguacagcau cggacuggca aucggaacaa acagcgucgg augggcaguc 60

aucacagacg aauacaaggu cccgagcaag aaguucaagg uccugggaaa cacagacaga	120
cacagcauca agaagaaccu gaucggagca cugcuguucg acagcggaga aacagcagaa	180
gcaacaagac ugaagagaac agcaagaaga agauacacaa gaagaaagaa cagaauucg	240
uaccugcagg aaaucuucag caacgaaaug gcaaaggucg acgacagcuu cuuccacaga	300
cuggaagaaa gcuuccuggu cgaagaagac aagaagcacg aaagacaccc gaucuucgga	360
aacaucgucg acgaagucgc auaccacgaa aaguacccga caaucuacca ccugagaaag	420
aagcuggucg acagcacaga caaggcagac cugagacuga ucuaccuggc acuggcacac	480
augaucaagu ucagaggaca cuuccugauc gaaggagacc ugaacccgga caacagcgac	540
gucgacaagc uguucaucca gcugguccag acauacaacc agcuguucga agaaaacccg	600
aucaacgcaa gcggagucga cgcaaaggca auccugagcg caagacugag caagagcaga	660
agacuggaaa accugaucgc acagcugccg ggagaaaaga agaacggacu guucggaaac	720
cugaucgcac ugagccuggg acugacaccg aacuucaaga gcaacuucga ccuggcagaa	780
gacgcaaagc ugcagcugag caaggacaca uacgacgacg accuggacaa ccugcuggca	840
cagaucggag accaguacgc agaccuguuc cuggcagcaa agaaccugag 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 aaucccgua uacgucggac cgcuggcaag aggaaacagc	1380
agauucgcau ggauagacaag aaagagcgaa gaaacaauca caccugggaa cuucgaagaa	1440
gucgucgaca agggagcaag cgcacagagc uucaucgaaa gaaugacaaa cuucgacaag	1500
aaccugccga acgaaaaggu ccugccgaag cacagccugc uguacgaaua cuucacaguc	1560
uacaacgaac ugacaaaggu caaguacguc acagaaggaa ugagaaagcc ggcauuccug	1620
agcggagaac agaagaaggc aaucgucgac cugcuguuca agacaaacag aaaggucaca	1680
gucaagcagc ugaaggaaga cuacuucaag aagaucgaau gcuucgacag cgucgaaauc	1740
agcggagucg aagacagauu caacgcaagc cugggaacau accacgaccu gcugaagauc	1800

aucaaggaca aggacuuccu ggacaacgaa gaaaacgaag acauccugga agacaucguc 1860
 cugacacuga cacuguucga agacagagaa augaucgaag aaagacugaa gacauacgca 1920
 caccuguucg acgacaaggu caugaagcag cugaagagaa gaagauacac aggaugggga 1980
 agacugagca gaaagcugau caacggaauc agagacaagc agagcggaaa gacaauccug 2040
 gacuuccuga agagcgacgg auucgcaaac agaaacuua ugcagcugau ccacgacgac 2100
 agccugacau ucaaggaaga cauccagaag gcacagguca gcggacaggg agacagccug 2160
 cacgaacaca ucgcaaaccu ggacaggaagc ccggcaauca agaagggaau ccugcagaca 2220
 gucaaggucg ucgacgaacu ggucaagguc augggaagac acaagccgga aaacaucguc 2280
 aucgaaaugg caagagaaaa ccagacaaca cagaagggac agaagaacag cagagaaaga 2340
 augaagagaa ucgaagaagg aaucaggaa cugggaagcc agauccugaa ggaacacccg 2400
 gucgaaaaca cacagcugca gaacgaaaag cuguaccugu acuaccugca gaacggaaga 2460
 gacauguacg ucgaccagga acuggacauc aacagacuga gcgacuacga cgucgaccac 2520
 aucguccgc agagcuuccu gaaggacgac agcaucgaca acaagguccu gacaagaagc 2580
 gacaagaaca gaggaagag cgacaacguc ccgagcgaag aagucgucaa gaagaugaag 2640
 aacuacugga gacagcugcu gaacgcaaag cugaucacac agagaaaguu cgacaaccug 2700

acaaaggcag agagaggagg acugagcgaa cuggacaagg caggauucau caagagacag 2760

cuggucgaaa caagacagau cacaaagcac gucgcacaga uccuggacag cagaaugaac 2820

acaaaguacg acgaaaacga caagcugauc agagaaguca aggucaucac acugaagagc 2880

aagcugguca gcgacuucag aaaggacuuc caguucuaca aggucaagaga aaucacaac 2940

uaccaccacg cacacgacgc auaccugaac gcagucgucg gaacagcacu gaucaagaag 3000

uaccgaagc uggaaagcga auucgucuac ggagacuaca agguacuaga cgucagaaag 3060

augaucgcaa agagcgaaca ggaaaucgga aaggcaacag caaguacuu cuucuacagc 3120

aacaucauga acuucuucac 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 gacagucga 3420

uacagcgucc uggucgucgc aaaggucgaa aagggaaga gcaagaagcu gaagagcguc 3480

aaggaacugc ugggaucac aaucaggaa 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 aagcacaag 4020
 gaaguccugg acgcaacacu gauccaccag agcaucacag gacuguacga aacaagaau 4080
 gaccugagcc agcugggagg 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 acccgacaa cagcgacguc 540

gacaagcugu ucauccagcu gguccagaca uacaaccagc uguucgaaga aaaccgauc 600

aacgcaagcg gagucgacgc aaaggcaauc cugagcgcaa gacugagcaa gagcagaaga 660

cuggaaaacc ugaucgcaca gcugccggga gaaaagaaga acggacuguu cggaaccug 720

aucgcacuga gccugggacu gacaccgaac uucaagagca acuucgaccu ggcagaagac 780

gcaaagcugc agcugagcaa ggacacauac gacgacgacc uggacaaccu gcuggcacag	840
aucgggagacc 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 aucgaugcu ucgacagcgu cgaaucagc 1740

ggagucgaag acagauuca cgcaagccug ggaacauacc acgaccugcu gaagaucauc 1800

aaggacaagg acuuccugga caacgaagaa aacgaagaca uccuggaaga caucguccug 1860

acacugacac uguucgaaga cagagaaaug aucgaagaaa gacugaagac auacgcacac 1920

cuguucgacg acaaggucan gaagcagcug aagagaagaa gauacacagg auggggaaga 1980

cugagcagaa agcugauca cggaaucaga gacaagcaga gcggaagac aaucgugac 2040

uuccugaaga gcgacggauu cgcaaacaga aacuucagc agcugauca cgacgacagc 2100

cugacauuca aggaagacau ccagaaggca caggucagcg gacagggaga cagccugac 2160

gaacacaucg caaaccuggc aggaagcccg gcaaucaaga agggaaucuu gcagacaguc 2220

aaggucgucg acgaacuggu caaggucan ggaagacaca agccggaaaa caucgucauc 2280

gaaauggcaa gagaaaacca gacaacacag aaggacaga agaacagcag agaaagaaug 2340

aagagaauucg aagaaggaa caaggaacug ggaagccaga uccugaagga acaccgguc 2400

gaaaacacac agcugcagaa cgaaaagcug uaccuguacu accugcagaa cggaagagac 2460

auguacgucg accaggaacu ggacaucaac agacugagcg acuacgacgu cgaccacau 2520

guccgcaga gcuuccugaa ggacgacagc aucgacaaca agguccugac aagaagcgac 2580
 aagaacagag gaaagagcga caacgucccg agcgaagaag ucgucaagaa gaugaagaac 2640
 uacuggagac agcugcugaa cgcaaagcug aucacacaga gaaaguucga caaccugaca 2700
 aaggcagaga gaggaggacu gagcgaacug gacaaggcag gauucaucaa gagacagcug 2760
 gucgaaacaa gacagaucac aaagcacguc gcacagaucc uggacagcag aaugaacaca 2820
 aaguacgacg aaaacgacaa gcugaucaga gaagucaagg ucaucacacu gaagagcaag 2880
 cuggucagcg acuucagaaa ggacuuccag uucuacaagg 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 agaaucaca cuggcaaagc 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 gagcgucaag 3480
 gaacugcugg gaaucacaau cauggaaaga agcagcuucg aaaagaaccc gaucgacuuc 3540
 cuggaagcaa agggauacaa ggaagucaag aaggaccuga ucaucaagcu gccgaaguac 3600
 agccguuucg aacuggaaaa cggaagaaag agaaucgugg caagcgagg agaacugcag 3660
 aagggaacg aacuggcacu gccgagcaag uacgucaacu uccuguaccu ggcaagccac 3720
 uacgaaaagc ugaagggaag cccggaagac aacgaacaga agcagcuguu cgucgaacag 3780
 cacaagcacu accuggacga aaucaucgaa cagaucagcg aaucagcaa gagagucauc 3840
 cuggcagacg caaaccugga caagguccug agcgcauaca acaagcacag agacaagccg 3900
 aucagagaac aggcagaaaa caucauccac cuguucacac ugacaaaccu gggagcaccg 3960
 gcagcauua aguacuucga cacaacauc gacagaaaga gauacacaag cacaaggaa 4020
 guccuggacg caacacugau ccaccagagc aucacaggac uguacgaaac aagaaucgac 4080
 cugagccagc ugaggaggaga c 4101

<210> 219

<211> 1368

<212> PRT

<213> Secuencia artificial

<220>

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

<400> 219

Met Asp Lys Lys Tyr Ser Ile Gly Leu Ala Ile Gly Thr Asn Ser Val

1 5 10 15

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

20 25 30

Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys Lys Asn Leu Ile

35 40 45

Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu

50 55 60

Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys

65 70 75 80

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

85 90 95

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

100 105 110

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

115 120 125

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

130 135 140

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

145 150 155 160

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

165 170 175

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

180 185 190

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

195 200 205

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

210 215 220

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

225 230 235 240

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

245 250 255

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

260 265 270

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

275 280 285

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

290 295 300

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

305 310 315 320

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

325

330

335

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

340

345

350

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

355

360

365

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

370

375

380

Gly Thr Glu Glu Leu Leu Val Lys Leu Asn Arg Glu Asp Leu Leu Arg

385

390

395

400

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

405

410

415

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

420

425

430

Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile

435 440 445

Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp

450 455 460

Met Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu

465 470 475 480

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

485 490 495

Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys Val Leu Pro Lys His Ser

500 505 510

Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu Leu Thr Lys Val Lys

515 520 525

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

530 535 540

Lys Lys Ala Ile Val Asp Leu Leu Phe Lys Thr Asn Arg Lys Val Thr

545 550 555 560

Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp

565 570 575

Ser Val Glu Ile Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu Gly

580 585 590

Thr Tyr His Asp Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp

595 600 605

Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile Val Leu Thr Leu Thr

610 615 620

Leu Phe Glu Asp Arg Glu Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala

625 630 635 640

His Leu Phe Asp Asp Lys Val Met Lys Gln Leu Lys Arg Arg Arg Tyr

645 650 655

Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp

660 665 670

Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe

675 680 685

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

690 695 700

Lys Glu Asp Ile Gln Lys Ala Gln Val Ser Gly Gln Gly Asp Ser Leu

705 710 715 720

His Glu His Ile Ala Asn Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly

725 730 735

Ile Leu Gln Thr Val Lys Val Val Asp Glu Leu Val Lys Val Met Gly

740 745 750

Arg His Lys Pro Glu Asn Ile Val Ile Glu Met Ala Arg Glu Asn Gln

755 760 765

Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu Arg Met Lys Arg Ile

770 775 780

Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile Leu Lys Glu His Pro

785 790 795 800

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

805 810 815

Gln Asn Gly Arg Asp Met Tyr Val Asp Gln Glu Leu Asp Ile Asn Arg

820 825 830

Leu Ser Asp Tyr Asp Val Asp Ala Ile Val Pro Gln Ser Phe Leu Lys

835 840 845

Asp Asp Ser Ile Asp Asn Lys Val Leu Thr Arg Ser Asp Lys Asn Arg

850 855 860

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

865 870 875 880

Asn Tyr Trp Arg Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys

885 890 895

Phe Asp Asn Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp

900

905

910

Lys Ala Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr

915

920

925

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

930

935

940

Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys Ser

945

950

955

960

Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys Val Arg

965

970

975

Glu Ile Asn Asn Tyr His His Ala His Asp Ala Tyr Leu Asn Ala Val

980

985

990

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

995

1000

1005

Val Tyr Gly Asp Tyr Lys Val Tyr Asp Val Arg Lys Met Ile Ala

1010 1015 1020

Lys Ser Glu Gln Glu Ile Gly Lys Ala Thr Ala Lys Tyr Phe Phe

1025 1030 1035

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

1040 1045 1050

Asn Gly Glu Ile Arg Lys Arg Pro Leu Ile Glu Thr Asn Gly Glu

1055 1060 1065

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

1070 1075 1080

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

1085 1090 1095

Glu Val Gln Thr Gly Gly Phe Ser Lys Glu Ser Ile Leu Pro Lys

1100 1105 1110

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

1115 1120 1125

Lys Lys Tyr Gly Gly Phe Asp Ser Pro Thr Val Ala Tyr Ser Val

1130 1135 1140

Leu Val Val Ala Lys Val Glu Lys Gly Lys Ser Lys Lys Leu Lys

1145 1150 1155

Ser Val Lys Glu Leu Leu Gly Ile Thr Ile Met Glu Arg Ser Ser

1160 1165 1170

Phe Glu Lys Asn Pro Ile Asp Phe Leu Glu Ala Lys Gly Tyr Lys

1175 1180 1185

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

1190 1195 1200

Phe Glu Leu Glu Asn Gly Arg Lys Arg Met Leu Ala Ser Ala Gly

1205 1210 1215

Glu Leu Gln Lys Gly Asn Glu Leu Ala Leu Pro Ser Lys Tyr Val

1220 1225 1230

Asn Phe Leu Tyr Leu Ala Ser His Tyr Glu Lys Leu Lys Gly Ser

1235

1240

1245

Pro Glu Asp Asn Glu Gln Lys Gln Leu Phe Val Glu Gln His Lys

1250

1255

1260

His Tyr Leu Asp Glu Ile Ile Glu Gln Ile Ser Glu Phe Ser Lys

1265

1270

1275

Arg Val Ile Leu Ala Asp Ala Asn Leu Asp Lys Val Leu Ser Ala

1280

1285

1290

Tyr Asn Lys His Arg Asp Lys Pro Ile Arg Glu Gln Ala Glu Asn

1295

1300

1305

Ile Ile His Leu Phe Thr Leu Thr Asn Leu Gly Ala Pro Ala Ala

1310

1315

1320

Phe Lys Tyr Phe Asp Thr Thr Ile Asp Arg Lys Arg Tyr Thr Ser

1325

1330

1335

Thr Lys Glu Val Leu Asp Ala Thr Leu Ile His Gln Ser Ile Thr

1340 1345 1350

Gly Leu Tyr Glu Thr Arg Ile Asp Leu Ser Gln Leu Gly Gly Asp

1355 1360 1365

<210> 220

<211> 4107

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 220

auggacaaga aguacagcau cggacuggca aucggaacaa acagcgucgg augggcaguc 60

aucacagacg aaaucaaggu cccgagcaag aaguucaagg uccugggaaa cacagacaga 120

cacagcauca agaagaaccu gaucggagca cugcuguucg acagcggaga aacagcagaa 180

gcaacaagac ugaagagaac agcaagaaga agauacacaa gaagaaagaa cagaaucugc 240

uaccugcagg aaaucuucag caacgaaaug gcaaaggucg acgacagcuu cuuccacaga 300

cuggaagaaa gcuuccuggu cgaagaagac aagaagcacg aaagacaccc gaucuucgga 360

aacaucgucg acgaagucgc auaccacgaa aaguacccga caaucuacca ccugagaaag	420
aagcuggucg acagcacaga caaggcagac cugagacuga ucuaccuggc acuggcacac	480
augaucaagu ucagaggaca cuuccugauc gaaggagacc ugaacccgga caacagcgac	540
gucgacaagc uguucaucca gcugguccag acauacaacc agcuguucga agaaaacccg	600
aucaacgcaa gcggagucga cgcaaaggca auccugagcg caagacugag caagagcaga	660
agacuggaaa accugaucgc acagcugccg ggagaaaaga agaacggacu guucggaaac	720
cugaucgcac ugagccuggg acugacaccg aacuucaaga gcaacuucga ccuggcagaa	780
gacgcaaagc ugcagcugag caaggacaca uacgacgacg accuggacaa ccugcuggca	840
cagaucggag accaguacgc agaccuguuc cuggcagcaa agaaccugag cgacgcauc	900
cugcugagcg acauccugag agucaacaca gaaucacaa aggcaccgcu gagcgcaagc	960
augaucaaga gauacgacga acaccaccag gaccugacac ugcugaaggc acuggucaga	1020
cagcagcugc cggaaaagua caaggaaauc uucuucgacc agagcaagaa cggauacgca	1080
ggauacaucg acggaggagc aagccaggaa gaauucuaca aguucauca gccgauccug	1140
gaaaagaugg acggaacaga agaacugcug gucaagcuga acagagaaga ccugcugaga	1200

aagcagagaa cauucgacaa cggaagcauc ccgcaccaga uccaccuggg agaacugcac 1260

gcaauccuga gaagacagga agacuucuac ccguuccuga aggacaacag agaaaagauc 1320

gaaaagaucc ugacauucag aaucccguaac uacgucggac cgcuggcaag aggaaacagc 1380

agauucgcau ggauagacaag aaagagcgaa gaaacaauca caccugggaa cuucgaagaa 1440

gucgucgaca agggagcaag cgcacagagc uucaucgaaa gaaugacaaa cuucgacaag 1500

aaccugccga acgaaaaggu ccugccgaag cacagccugc uguacgaaua cuucacaguc 1560

uacaacgaac ugacaaaggu caaguacguc acagaaggaa ugagaaagcc ggcauuccug 1620

agcggagaac agaagaaggc aaucgucgac cugcuguuca agacaaacag aaaggucaca 1680

gucaagcagc ugaaggaaga cuacuuaag aagaucgaau gcuucgacag cgucgaaauc 1740

agcggagucg aagacagauu caacgcaagc cugggaacau accacgaccu gcugaagauc 1800

aucaaggaca aggacuuccu ggacaacgaa gaaaacgaag acauccugga agacaucguc 1860

cugacacuga cacuguucga agacagagaa augaucgaag aaagacugaa gacauacgca 1920

caccuguucg acgacaaggu caugaagcag cugaagagaa gaagauacac aggaugggga 1980

agacugagca gaaagcugau caacggaauc agagacaagc agagcggaag gacaauccug 2040

gacuuccuga agagcgacgg auucgcaaac agaaacuua 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 aaucaggaa 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 gaggaagag cgacaacguc ccgagcgaag aagucgucaa gaagaugaag 2640

aacuacugga gacagcugcu gaacgcaaag cugaucacac agagaaaguu cgacaaccug 2700

acaaaggcag agagaggagg acugagcgaa cuggacaagg caggauucau caagagacag 2760

cuggucgaaa caagacagau cacaagcac gucgcacaga uccuggacag cagaaugaac 2820

acaaaguacg acgaaaacga caagcugauc agagaaguca aggucaucac acugaagagc 2880

aagcugguca gcgacuucag aaaggacuuc caguucuaca aggucagaga 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 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 gaagagcuc 3480

aaggaacugc ugggaaucaac aaucaggaa agaagcagcu ucgaaaagaa cccgaucgac 3540

uuccuggaag caaagggaau caaggaaguc aagaaggacc ugaucaucaa gcugccgaag 3600

uacagccugu ucgaacugga aaacggaaga aagagaauvc uggcaagcgc aggagaacug 3660

cagaagggaac acgaacuggc acugccgagc aaguacguca acuuccugua ccuggcaagc 3720

cacuacgaaa agcugaaggg aagcccgga 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 agacuag 4107

<210> 221

<211> 4113

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 221

gacaagaagu acagcaucgg acuggcaauc ggaacaaaca gcgucggaug ggcagucauc 60

acagacgaau acaaggucc 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 ggagaccug agacugaucu accuggcacu ggcacacaug	480
aucaaguuca gaggacacuu ccugaucgaa ggagaccuga acccggacaa cagcgacguc	540
gacaagcugu ucauccagcu gguccagaca uacaaccagc uguucgaaga aaaccgauc	600
aacgcaagcg gagucgacgc aaaggcaauc cugagcgcaa gacugagcaa gagcagaaga	660
cuggaaaacc ugaucgcaca gcugccggga gaaaagaaga acggacuguu cggaaccug	720
aucgcacuga gccugggacu gacaccgaac uucaagagca acuucgaccu 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 gagtagcaag 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 cgaaucagc 1740

ggagucgaag acagauuca cgcaagccug ggaacauacc acgaccugcu gaagaucauc 1800

aaggacaagg acuuccugga caacgaagaa aacgaagaca uccuggaaga caucguccug 1860

acacugacac uguucgaaga cagagaaaug aucgaagaaa gacugaagac auacgcacac 1920

cuguucgacg acaaggucau gaagcagcug aagagaagaa gauacacagg auggggaaga 1980

cugagcagaa agcugaucaa cggaaucaga gacaagcaga gcggaaagac aauccuggac 2040

uuccugaaga gcgacggauu cgaaacaga 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 aagggacaga agaacagcag agaaagaug 2340

aagagaauucg aagaaggaa ucaaggaacug 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 caacguccg agcgaagaag ucgucaagaa gaugaagaac 2640

uacuggagac agcugcugaa cgaaagcug aucacacaga gaaaguucga caaccugaca 2700

aaggcagaga gaggaggacu gagcgaacug gacaaggcag gauucauaa gagacagcug 2760

gucgaaacaa gacagaucac aaagcagcug gcacagauc 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 agaaucaca 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 gagcgucaag 3480
gaacugcugg gaaucacaau cauggaaaga agcagcuucg aaaagaaccc gaucgacuuc 3540
cuggaagcaa agggauacaa ggaagucaag aaggaccuga ucaucaagcu gccgaaguac 3600
agccuguucg aacuggaaaa cggaagaaag agaaugcugg caagcgagg agaacugcag 3660

aagggaacg aacuggcacu gccgagcaag uacgucaacu uccuguaccu ggcaagccac 3720

uacgaaaagc ugaagggaag cccggaagac aacgaacaga agcagcuguu cgucgaacag 3780

cacaagcacu accuggacga aaucaucgaa cagaucagcg aaucagcaa gagagucauc 3840

cuggcagacg caaaccugga caagguccug agcgcauaca acaagcacag agacaagccg 3900

aucagagaac aggcagaaaa caucauccac cuguucacac ugacaaaccu gggagcaccg 3960

gcagcauua aguacuucga cacaacaauc gacagaaaga gauacacaag cacaaggaa 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

aacaucgucg acgaagucgc auaccacgaa aaguacccga caaucuacca ccugagaaag	420
aagcuggucg acagcacaga caaggcagac cugagacuga ucuaccuggc acuggcacac	480
augaucaagu ucagaggaca cuuccugauc gaaggagacc ugaacccgga caacagcgac	540
gucgacaagc uguucaucca gcugguccag acauacaacc agcuguucga agaaaacccg	600
aucaacgcaa gcggagucga cgcaaaggca auccugagcg caagacugag caagagcaga	660
agacuggaaa accugaucgc acagcugccg ggagaaaaga agaacggacu guucggaaac	720
cugaucgcac ugagccuggg acugacaccg aacuucaaga gcaacuucga ccuggcagaa	780
gacgcaaagc ugcagcugag caaggacaca uacgacgacg accuggacaa ccugcuggca	840
cagaucggag accaguacgc agaccuguuc cuggcagcaa agaaccugag cgacgcauc	900
cugcugagcg acauccugag agucaacaca gaaucacaa aggcaccgcu gagcgcaagc	960
augaucaaga gauacgacga acaccaccag gaccugacac ugcugaaggc acuggucaga	1020
cagcagcugc cggaaaagua caaggaaauc uucuucgacc agagcaagaa cggauacgca	1080
ggauacaucg acggaggagc aagccaggaa gaauucuaca aguucauca gccgauccug	1140
gaaaagaugg acggaacaga agaacugcug gucaagcuga acagagaaga ccugcugaga	1200
aagcagagaa cauucgacaa cggaagcauc ccgcaccaga uccaccuggg agaacugcac	1260

gcaauccuga gaagacagga agacuucua cccuuccuga aggacaacag agaaaagauc 1320

gaaaagaucc ugacauucag aaucgccuac uacgucggac cgcuggcaag aggaaacagc 1380

agauucgcau ggaugacaag aaagagcgaa gaaacaauca caccugggaa cuucgaagaa 1440

gucgucgaca agggagcaag cgcacagagc uucaucgaaa gaaugacaaa cuucgacaag 1500

aaccugccga acgaaaaggu ccugccgaag cacagccugc uguacgaaua cuucacaguc 1560

uacaacgaac ugacaaaggu caaguacguc acagaaggaa ugagaaagcc ggcauuccug 1620

agcggagaac agaagaaggc aaucgucgac cugcuguuca agacaaacag aaaggucaca 1680

gucaagcagc ugaaggaaga cuacuuaag aagaucgaau gcuucgacag cgucgaaauc 1740

agcggagucg aagacagauu caacgcaagc cugggaacau accacgaccu gcugaagauc 1800

aucaaggaca aggacuuccu ggacaacgaa gaaaacgaag acauccugga agacaucguc 1860

cugacacuga cacuguucga agacagagaa augaucgaag aaagacugaa gacauacgca 1920

caccuguucg acgacaaggu caugaagcag cugaagagaa gaagauacac aggaugggga 1980

agacugagca gaaagcugau caacggaauc agagacaagc agagcggaag gacaauccug 2040

gacuuccuga agagcgacgg auucgcaaac agaaacuua ugcagcugau ccacgacgac 2100

agccugacau ucaaggaaga cauccagaag gcacagguca gcggacaggg agacagccug 2160

cacgaacaca ucgcaaaccu ggcaaggaagc ccggcaauca agaagggaau ccugcagaca 2220

gucaaggucg ucgacgaacu ggucaagguc augggaagac acaagccgga aaacaucguc 2280

aucgaaaugg caagagaaaa ccagacaaca cagaagggaac agaagaacag cagagaaaga 2340

augaagagaa ucgaagaagg aaucaggaa cugggaagcc agauccugaa ggaacacccg 2400

gucgaaaaca cacagcugca gaacgaaaag cuguaccugu acuaccugca gaacggaaga 2460

gacauguacg ucgaccagga acuggacauc aacagacuga gcgacuacga cgucgaccac 2520

aucguccgc agagcuuccu gaaggacgac agcaucgaca acaagguccu gacaagaagc 2580

gacaagaaca gaggaagag cgacaacguc ccgagcgaag aagucgucaa gaagaugaag 2640

aacuacugga gacagcugcu gaacgcaaag cugaucacac agagaaaguu cgacaaccug 2700

acaaaggcag agagaggagg acugagcgaa cuggacaagg caggauucau caagagacag 2760

cuggucgaaa caagacagau cacaagcac gucgcacaga uccuggacag cagaaugaac 2820

acaaaguacg acgaaaacga caagcugauc agagaaguca aggucaucac acugaagagc 2880

aagcugguca gcgacuucag aaaggacuuc caguucuaca aggucagaga aaucacaac 2940

uaccaccacg cacacgacgc auaccugaac gcagucgucg gaacagcacu gaucaagaag 3000

uacccgaagc uggaagcga auucgucuac ggagacuaca aggucuacga cgucagaaag 3060

augaucgcaa agagcgaaca ggaaaucgga aaggcaacag caaaguacuu cuucuacagc 3120

aacaucauga acuucuucaa 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 ugguucgucg aaaggucgaa aagggaaga gcaagaagcu gaagagcguc 3480

aaggaacugc uggaauac aaucuggaa agaagcagcu ucgaaaagaa cccgaucgac 3540

uuccuggaag caaagggaau caaggaaguc aagaaggacc ugaucauaa gcugccgaag 3600

uacagccugu ucgaacugga aaacggaaga aagagaaucg uggaagcgc aggagaacug 3660

cagaaggga acgaacuggc acugccgagc aaguacguca acuuccugua ccuggcaagc 3720

cacuacgaaa agcugaaggg aagcccgga gacaacgaac agaagcagcu guucgucgaa 3780

cagcacaagc acuaccugga cgaaaaucau 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 aacaagauc 4080

gaccugagcc agcuggggagg agacggagga ggaagcccga agaagaagag aaaggucccg 4140

aagaagaaga gaaaggucgg aagcggaagc ccgaagaaga agagaaaggu cgacggaagc 4200

ccgaagaaga agagaaaggu cgacagcgga uag 4233

<210> 224

<211> 4227

<212> ARN

<213> Secuencia artificial

<220>

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

<400> 224

gacaagaagu acagcaucgg acuggacauc ggaacaaaca gcgucggaug ggcagucauc 60

acagacgaau acaaggucc gagcaagaag uucaaggucc ugaggaaacac agacagacac 120

agcaucaaga agaaccugau cggagcacug cuguucgaca gcggagaaac agcagaagca	180
acaagacuga agagaacagc aagaagaaga uacacaagaa gaaagaacag aaucugcuac	240
cugcaggaaa ucuucagcaa cgaaauggca aaggucgacg acagcuucuu ccacagacug	300
gaagaaagcu uccuggucga agaagacaag aagcacgaaa gacacccgau cuucggaaac	360
aucgucgacg aagucgcaua ccacgaaaag uaccgacaa ucuaccaccu gagaaagaag	420
cuggucgaca gcacagacaa ggacagaccug agacugaucu accuggcacu ggcacacaug	480
aucaaguuca gaggacacuu ccugaucgaa ggagaccuga acccggacaa cagcgacguc	540
gacaagcugu ucauccagcu guccagaca uacaaccagc uguucgaaga aaaccgauc	600
aacgcaagcg gagucgacgc aaaggcauc cugagcgcaa gacugagcaa gagcagaaga	660
cuggaaaacc ugaucgcaca gcugccggga gaaaagaaga acggacuguu cggaaccug	720
aucgcacuga gccugggacu gacaccgaac uucaagagca acuucgaccu ggcagaagac	780
gcaaagcugc agcugagcaa ggacacauac gacgacgacc uggacaaccu gcuggcacag	840
aucggagacc aguacgcaga ccuguuccug gcagcaaaga accugagcga cgcaauccug	900
cugagcgaca uccugagagu caacacagaa aucacaaagg caccgcugag cgcaagcaug	960

aucaagagau acgacgaaca ccaccaggac cugacacugc ugaaggcacu ggucagacag 1020

 cagcugccgg aaaaguacaa ggaaaucuuc uucgaccaga gcaagaacgg auacgcagga 1080

 ucaucgacg gaggagcaag ccaggaagaa uucuacaagu ucaucaagcc gaucuggaa 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 acauacacac cguggaacuu cgaagaaguc 1440

 gucgacaagg gagcaagcgc acagagcuuc aucgaaagaa ugacaaacuu cgacaagaac 1500

 cugccgaacg aaaagguccu gccgaagcac agccugcugu acgaauacuu cacagucuac 1560

 aacgaacuga caaaggucaa guacgucaca gaaggaauga gaaagccggc auuccugagc 1620

 ggagaacaga agaaggcaau cgucgaccug cuguucaaga caaacagaaa ggucacaguc 1680

 aagcagcuga aggaagacua cuucaagaag aucgaaugcu ucgacagcgu cgaaaucagc 1740

 ggagucgaag acagauucaa cgcaagccug ggaacauacc acgaccugcu gaagaucauc 1800

 aaggacaagg acuuccugga caacgaagaa aacgaagaca uccuggaaga caucguccug 1860

acacugacac uguucgaaga cagagaaaug aucgaagaaa gacugaagac auacgcacac 1920

cuguucgacg acaaggucan gaagcagcug aagagaagaa gauacacagg auggggaaga 1980

cugagcagaa agcugaucaa cggaaucaga gacaagcaga gcggaaagac aaucuggac 2040

uuccugaaga gcgacggauu cgcaaacaga aacuucaugc agcugaucca cgacgacagc 2100

cugacauuca aggaagacau ccagaaggca caggucagcg gacagggaga cagccugcac 2160

gaacacaucg caaaccuggc aggaagcccg gcaaucaaga agggaaucuu gcagacaguc 2220

aaggucgucg acgaacuggu caaggucaug ggaagacaca agccggaaaa caucgucauc 2280

gaaauggcaa gagaaaacca gacaacacag aaggagcaga agaacagcag agaaagaau 2340

aagagaauucg aagaaggaa caaggaucg ggaagccaga uccugaagga acaccgguc 2400

gaaaacacac agcugcagaa cgaaaagcug uaccuguacu accugcagaa cggaagagac 2460

auguacgucg accaggaacu ggacaucaac agacugagcg acucgacgu cgaccacau 2520

guccgcaga gcuuccugaa ggacgacagc aucgacaaca agguccugac aagaagcgac 2580

aagaacagag gaaagagcga caacugcccg agcgaagaag ucgucaagaa gaugaagaac 2640

uacuggagac agcugcugaa cgaaaagcug aucacacaga gaaaguucga caaccugaca 2700

aaggcagaga gaggaggacu gagcgaacug gacaaggcag gauucauca 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 cagaaaug 3060

aucgcaaaga gcgaacagga aaucggaaag gcaacagcaa aguacuucuu cuacagcaac 3120

aucaugaacu ucuucaagac agaaucaca cuggcaaacg gagaaucag aaagagaccg 3180

cugaucgaaa caaacggaga aacaggagaa aucgucuggg acaagggaag agacuucgca 3240

acagucagaa agguccugag caugccgcag gucaacaucg ucaagaagac agaaguccag 3300

acaggaggau ucagcaagga aagcauccug ccgaagagaa acagcgacaa gcugaucgca 3360

agaaagaagg acugggaccc gaagaaguac ggaggauucg acagcccgac agucgcauac 3420

agcguccugg ucgucgcaaa ggucgaaaag ggaaagagca agaagcugaa gagcgucaag 3480

gaacugcugg gaaucacau cauggaaaga agcagcuucg aaaagaaccc gaucgacuuc 3540

cuggaagcaa agggauacaa ggaagucaag aaggaccuga ucaucaagcu gccgaaguac 3600

agccuguucg aacuggaaaa cggaagaaag agaaugcugg caagcgagg agaacugcag	3660
aagggaacg aacuggcacu gccgagcaag uacgucaacu uccuguaccu ggcaagccac	3720
uacgaaaagc ugaagggaag cccggaagac aacgaacaga agcagcuguu cgucgaacag	3780
cacaagcacu accuggacga aaucaucgaa cagaucagcg aaucagcaa gagagucauc	3840
cuggcagacg caaaccugga caagguccug agcgcauaca acaagcacag agacaagccg	3900
aucagagaac aggcagaaaa caucauccac cuguucacac ugacaaaccu gggagcaccg	3960
gcagcauua aguacuucga cacaacaauc gacagaaaga gauacacaag caaaaggaa	4020
guccuggacg caacacugau ccaccagagc aucacaggac uguacgaaac aagaaucgac	4080
cugagccagc ugggaggaga cggaggagga agcccgaaga agaagagaaa ggucccgaag	4140
aagaagagaa aggucggaag cggaagcccg aagaagaaga gaaaggucga cggaagcccg	4200
aagaagaaga gaaaggucga cagcgga	4227

<210> 225

<211> 1392

<212> PRT

<213> Secuencia artificial

<220>

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

<400> 225

Met Asp Lys Lys Tyr Ser Ile Gly Leu Ala Ile Gly Thr Asn Ser Val

1 5 10 15

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

20 25 30

Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys Lys Asn Leu Ile

35 40 45

Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu

50 55 60

Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys

65 70 75 80

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

85 90 95

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

100

105

110

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

115

120

125

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

130

135

140

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

145

150

155

160

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

165

170

175

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

180

185

190

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

195

200

205

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

210 215 220

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

225 230 235 240

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

245 250 255

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

260 265 270

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

275 280 285

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

290 295 300

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

305 310 315 320

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

325 330 335

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

340 345 350

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

355 360 365

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

370 375 380

Gly Thr Glu Glu Leu Leu Val Lys Leu Asn Arg Glu Asp Leu Leu Arg

385 390 395 400

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

405 410 415

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

420 425 430

Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile

435 440 445

Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp

450

455

460

Met Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu

465

470

475

480

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

485

490

495

Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys Val Leu Pro Lys His Ser

500

505

510

Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu Leu Thr Lys Val Lys

515

520

525

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

530

535

540

Lys Lys Ala Ile Val Asp Leu Leu Phe Lys Thr Asn Arg Lys Val Thr

545

550

555

560

Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp

565

570

575

Ser Val Glu Ile Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu Gly

580

585

590

Thr Tyr His Asp Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp

595

600

605

Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile Val Leu Thr Leu Thr

610

615

620

Leu Phe Glu Asp Arg Glu Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala

625

630

635

640

His Leu Phe Asp Asp Lys Val Met Lys Gln Leu Lys Arg Arg Arg Tyr

645

650

655

Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp

660

665

670

Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe

675 680 685

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

690 695 700

Lys Glu Asp Ile Gln Lys Ala Gln Val Ser Gly Gln Gly Asp Ser Leu

705 710 715 720

His Glu His Ile Ala Asn Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly

725 730 735

Ile Leu Gln Thr Val Lys Val Val Asp Glu Leu Val Lys Val Met Gly

740 745 750

Arg His Lys Pro Glu Asn Ile Val Ile Glu Met Ala Arg Glu Asn Gln

755 760 765

Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu Arg Met Lys Arg Ile

770 775 780

Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile Leu Lys Glu His Pro

785 790 795 800

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

805 810 815

Gln Asn Gly Arg Asp Met Tyr Val Asp Gln Glu Leu Asp Ile Asn Arg

820 825 830

Leu Ser Asp Tyr Asp Val Asp His Ile Val Pro Gln Ser Phe Leu Lys

835 840 845

Asp Asp Ser Ile Asp Asn Lys Val Leu Thr Arg Ser Asp Lys Asn Arg

850 855 860

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

865 870 875 880

Asn Tyr Trp Arg Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys

885 890 895

Phe Asp Asn Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp

900 905 910

Lys Ala Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr

915 920 925

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

930 935 940

Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys Ser

945 950 955 960

Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys Val Arg

965 970 975

Glu Ile Asn Asn Tyr His His Ala His Asp Ala Tyr Leu Asn Ala Val

980 985 990

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

995 1000 1005

Val Tyr Gly Asp Tyr Lys Val Tyr Asp Val Arg Lys Met Ile Ala

1010 1015 1020

Lys Ser Glu Gln Glu Ile Gly Lys Ala Thr Ala Lys Tyr Phe Phe

1025 1030 1035

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

1040 1045 1050

Asn Gly Glu Ile Arg Lys Arg Pro Leu Ile Glu Thr Asn Gly Glu

1055 1060 1065

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

1070 1075 1080

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

1085 1090 1095

Glu Val Gln Thr Gly Gly Phe Ser Lys Glu Ser Ile Leu Pro Lys

1100 1105 1110

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

1115 1120 1125

Lys Lys Tyr Gly Gly Phe Asp Ser Pro Thr Val Ala Tyr Ser Val

1130 1135 1140

Leu Val Val Ala Lys Val Glu Lys Gly Lys Ser Lys Lys Leu Lys

1145 1150 1155

Ser Val Lys Glu Leu Leu Gly Ile Thr Ile Met Glu Arg Ser Ser

1160 1165 1170

Phe Glu Lys Asn Pro Ile Asp Phe Leu Glu Ala Lys Gly Tyr Lys

1175 1180 1185

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

1190 1195 1200

Phe Glu Leu Glu Asn Gly Arg Lys Arg Met Leu Ala Ser Ala Gly

1205 1210 1215

Glu Leu Gln Lys Gly Asn Glu Leu Ala Leu Pro Ser Lys Tyr Val

1220 1225 1230

Asn Phe Leu Tyr Leu Ala Ser His Tyr Glu Lys Leu Lys Gly Ser

1235 1240 1245

Pro Glu Asp Asn Glu Gln Lys Gln Leu Phe Val Glu Gln His Lys

1250 1255 1260

His Tyr Leu Asp Glu Ile Ile Glu Gln Ile Ser Glu Phe Ser Lys

1265 1270 1275

Arg Val Ile Leu Ala Asp Ala Asn Leu Asp Lys Val Leu Ser Ala

1280 1285 1290

Tyr Asn Lys His Arg Asp Lys Pro Ile Arg Glu Gln Ala Glu Asn

1295 1300 1305

Ile Ile His Leu Phe Thr Leu Thr Asn Leu Gly Ala Pro Ala Ala

1310 1315 1320

Phe Lys Tyr Phe Asp Thr Thr Ile Asp Arg Lys Arg Tyr Thr Ser

1325 1330 1335

Thr Lys Glu Val Leu Asp Ala Thr Leu Ile His Gln Ser Ile Thr

1340 1345 1350

Gly Leu Tyr Glu Thr Arg Ile Asp Leu Ser Gln Leu Gly Gly Asp

1355

1360

1365

Gly Ser Gly Ser Pro Lys Lys Lys Arg Lys Val Asp Gly Ser Pro

1370

1375

1380

Lys Lys Lys Arg Lys Val Asp Ser Gly

1385

1390

<210> 226

<211> 4179

<212> ARN

<213> Secuencia artificial

<220>

<223> Sintético: ORF del ARNm de la nickasa Cas9 que codifica la SEQ ID NO: 25 que usa
codones de mínima uridina como se enumeran en la Tabla 3, sin codones
de inicio y parada

<400> 226

auggacaaga aguacagcau cggacuggca aucggaacaa acagcgucgg augggcaguc 60

aucacagacg aauacaaggu cccgagcaag aaguucaagg uccugggaaa cacagacaga 120

cacagcauca agaagaaccu gaucggagca cugcuguucg acagcggaga aacagcagaa	180
gcaacaagac ugaagagaac agcaagaaga agauacacaa gaagaaagaa cagaaucugc	240
uaccugcagg aaaucuucag caacgaaaug gcaaaggucg acgacagcuu cuuccacaga	300
cuggaagaaa gcuuccuggu cgaagaagac aagaagcacg aaagacaccc gaucuucgga	360
aacaucgucg acgaagucgc auaccacgaa aaguacccga caaucuacca ccugagaaaag	420
aagcuggucg acagcacaga caaggcagac cugagacuga ucuaccuggc acuggcacac	480
augaucaagu ucagaggaca cuuccugauc gaaggagacc ugaacccgga caacagcgac	540
gucgacaagc uguucaucca gcugguccag acauacaacc agcuguucga agaaaacccg	600
aucaacgcaa gcggagucga cgcaaaggca auccugagcg caagacugag caagagcaga	660
agacuggaaa accugaucgc acagcugccg ggagaaaaga agaacggacu guucggaaac	720
cugaucgcac ugagccuggg acugacaccg aacuucaaga gcaacuucga ccuggcagaa	780
gacgcaaagc ugcagcugag caaggacaca uacgacgacg accuggacaa ccugcuggca	840
cagaucggag accaguacgc agaccuguuc cuggcagcaa agaaccugag cgacgcaauc	900
cugcugagcg acauccugag agucaacaca 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 cauucgacaa cggaagcauc ccgcaccaga uccaccuggg agaacugcac 1260

gcaauccuga gaagacagga agacuucuac ccguuccuga aggacaacag agaaaagauc 1320

gaaaagaucc ugacauucag aaucccguac uacgucggac cgcuggcaag aggaaacagc 1380

agauucgcau ggaugacaag aaagagcgaa gaaacaauca caccugggaa cuucgaagaa 1440

gucgucgaca agggagcaag cgcacagagc uucaucgaaa gaaugacaaa cuucgacaag 1500

aaccugccga acgaaaaggu ccugccgaag cacagccugc uguacgaaua cuucacaguc 1560

uacaacgaac ugacaaaggu caaguacguc acagaaggaa ugagaaagcc ggcauuccug 1620

agcggagAAC agaagaaggc aaucgucgac cugcuguuca agacaaacag aaaggucaca 1680

gucaagcagc ugaaggaaga cuacuuaag aagaucgaau gcuucgacag cgucgaaauc 1740

agcggagucg aagacagauu caacgcaagc cugggaacau accacgaccu gcugaagauc 1800

aucaaggaca aggacuuccu ggacaacgaa gaaaacgaag acauccugga agacaucguc 1860

cugacacuga cacuguucga agacagagaa augaucgaag aaagacugaa gacauacgca 1920

caccuguucg acgacaaggu caugaagcag cugaagagaa gaagauacac aggaugggga 1980

agacugagca gaaagcugau caacggauc agagacaagc agagcggaaa gacaauccug 2040

gacuuccuga agagcgacgg auucgcaaac agaaacuua ugcagcugau ccacgacgac 2100

agccugacau ucaaggaaga cauccagaag gcacagguca gcggacaggg agacagccug 2160

cacgaacaca ucgcaaaccu ggaggaagc ccggcaauca agaagggaau ccugcagaca 2220

gucaaggucg ugcacgaacu ggucaagguc augggaagac acaagccgga aaacaucguc 2280

aucgaaaugg caagagaaaa ccagacaaca cagaagggac agaagaacag cagagaaaga 2340

augaagagaa ucgaagaagg aaucaggaa cugggaagcc agauccugaa ggaacaccg 2400

gucgaaaaca cacagcugca gaacgaaaag cuguaccugu acuaccugca gaacggaaga 2460

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gacaagaaca gaggaagag cgacaacguc ccgagcgaag aagucgucaa gaagaugaag 2640

aacuacugga gacagcugcu gaacgcaaag cugaucacac agagaaaguu cgacaaccug 2700

acaaaggcag agagaggagg acugagcgaa cuggacaagg caggauucau caagagacag 2760

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aagcugguca gcgacuucag aaaggacuuc caguucuaca agguagaga aaaucaaac 2940

uaccaccacg cacacgacgc auaccugaac gcagucgucg gaacagcacu gaucaagaag 3000

uaccgaagc uggaaagcga auucgucuac ggagacuaca agguacuaga cgucagaaag 3060

augaucgcaa agagcgaaca ggaaucgga aaggcaacag caaaguacuu cuucuacagc 3120

aacauauga acuucuuaa gacagaaauc acacuggcaa acggagaaaau cagaaagaga 3180

ccgcugaucg aaacaaacgg agaaacagga gaaucgucu gggacaaggg aagagacuuc 3240

gcaacaguca gaaagguccu gagcaugccg caggucaaca ucgucaagaa gacagaaguc 3300

cagacaggag gauucagcaa ggaaagcauc cugccgaaga gaaacagcga caagcugauc 3360

gcaagaaaga aggacuggga cccgaagaag uacggaggau ucgacagccc gacagucgca 3420

uacagcgucc uggucgucg aaaggucgaa aagggaaga gcaagaagcu gaagagcguc 3480

aaggaacugc ugggaauac aaucaggaa agaagcagcu ucgaaaagaa ccgcaucgac 3540

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uacagccugu ucgaacugga aaacggaaga aagagaaugc uggcaagcgc aggagaacug 3660
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 cacuacgaaa agcugaaggg aagcccggaa gacaacgaac agaagcagcu guucgucgaa 3780
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 ccggcagcau ucaaguacuu cgacacaaca aucgacagaa agagauacac aagcacaag 4020
 gaaguccugg acgcaacacu gauccaccag agcaucacag gacuguacga aacaagauc 4080
 gaccugagcc agcuggggagg 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

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

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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
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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
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aaggacaagg acuuccugga caacgaagaa aacgaagaca uccuggaaga caucguccug 1860
acacugacac uguucgaaga cagagaaaug aucgaagaaa gacugaagac auacgcacac 1920
cuguucgacg acaaggucan gaagcagcug aagagaagaa gauacacagg auggggaaga 1980
cugagcagaa agcugaucaa cggaaucaaga gacaagcaga gcggaaagac aauccuggac 2040
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cugacauuca aggaagacau ccagaaggca caggucagcg gacagggaga cagccugcac 2160
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 aucgcaaaga gcgaacagga aaucggaaag gcaacagcaa aguacuucuu cuacagcaac 3120

 aucaugaacu ucuucaagac agaaucaca cuggcaaacg gagaaucag aaagagaccg 3180

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 aucagagaac aggcagaaaa caucauccac cuguucacac ugacaaaccu gggagcaccg 3960
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 cugagccagc ugggaggaga cggaagcgga agcccgaaga agaagagaaa ggucgacgga 4140
 agcccgaaga agaagagaaa ggucgacagc gga 4173

<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

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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
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augaucaagu ucagaggaca cuuccugauc gaaggagacc ugaacccgga caacagcgac	540
gucgacaagc uguucaucca gcugguccag acauacaacc agcuguucga agaaaacccg	600
aucaacgcaa gcgagucga cgcaaaggca auccugagcg caagacugag caagagcaga	660
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cugaucgcac ugagccuggg acugacaccg aacuuaaga gcaacuucga ccuggcagaa	780
gacgcaaagc ugcagcugag caaggacaca uacgacgacg accuggacaa ccugcuggca	840
cagaucggag accaguacgc agaccuguuc cuggcagcaa agaaccugag cgacgcaauc	900

cugcugagcg acauccugag agucaacaca gaaaucacaa aggcaccgcu gagcgcaagc 960

augaucaaga gauacgacga acaccaccag gaccugacac ugcugaaggc acuggucaga 1020

cagcagcugc cggaaaagua caaggaaauc uucuucgacc agagcaagaa cggauacgca 1080

ggauacaucg acggaggagc aagccaggaa gaauucuaca aguucauaa gccgauccug 1140

gaaaagaugg acggaacaga agaacugcug gucaagcuga acagagaaga ccugcugaga 1200

aagcagagaa cauucgacaa cggaagcauc ccgcaccaga uccaccuggg agaacugcac 1260

gcaauccuga gaagacagga agacuucuac ccguuccuga aggacaacag agaaaagauc 1320

gaaaagaucc ugacauucag aaucccgua uacgucggac cgcuggcaag aggaaacagc 1380

agauucgau ggauagacaag aaagagcgaa gaaacaauc caccugggaa cuucgaagaa 1440

gucgucgaca agggagcaag cgcacagagc uucaucgaaa gaaugacaaa cuucgacaag 1500

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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

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gucgaaaaca cacagcugca gaacgaaaag cuguaccugu acuaccugca gaacggaaga 2460

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gacaagaaca gaggaaagag cgacaacguc ccgagcgaag aagucgucaa gaagaugaag 2640

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aacauauga acuucucaa gacagaaauc acacuggcaa acggagaaau cagaaagaga 3180

ccgcugaucg aaacaaacgg agaaacagga gaaucgucu gggacaaggg aagagacuuc 3240

gcaacaguca gaaagguccu gagcaugccg caggucaaca ucgucaagaa gacagaaguc 3300

cagacaggag gauucagcaa ggaaagcauc cugccgaaga gaaacagcga caagcugauc 3360

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ccgaucagag aacaggcaga aaacaucauc caccuguuca cacugacaaa ccugggagca 3960

ccggcagcau ucaaguacuu cgacacaaca aucgacagaa agagauacac aagcacaag 4020

gaaguccugg acgcaacacu gauccaccag agcaucacag gacuguacga aacaagaau 4080

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ggaagcccga agaagaagag aaaggucgac agcggauag 4179

<210> 230

<211> 4173

<212> ARN

<213> Secuencia artificial

<220>

<223> Sintético: secuencia de codificación de dCas9 que codifica la SEQ ID NO: 228 que usa codones de mínima uridina (sin codones de inicio y parada; adecuada para su inclusión en la secuencia de codificación de proteínas de fusión)

<400> 230

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agcaucaaga agaaccugau cggagcacug cuguucgaca gcggagaaac agcagaagca 180

acaagacuga agagaacagc aagaagaaga uacacaagaa gaaagaacag aaucugcuac 240

cugcaggaaa ucuucagcaa 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 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
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uucgcaugga ugacaagaaa gagcgaagaa acaucacac cguggaacuu cgaagaaguc	1440
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acacugacac uguucgaaga cagagaaaug aucgaagaaa gacugaagac auacgcacac 1920

cuguucgacg acaaggucau gaagcagcug aagagaagaa gauacacagg auggggaaga 1980

cugagcagaa agcugaucaa cggaaucaaga gacaagcaga gcggaaagac aauccuggac 2040

uuccugaaga gcgacggauu cgcaaacaga aacucaugc agcugaucca cgacgacagc 2100

cugacauuca aggaagacau ccagaaggca caggucagcg gacagggaga cagccugcac 2160

gaacacaucg caaaccuggc aggaagcccg gcaaucaaga agggaauccu gcagacaguc 2220

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gaaauggcaa gagaaaacca gacaacacag aaggacaga agaacagcag agaaagaug 2340

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gaaaacacac agcugcagaa cgaaaagcug uaccuguacu accugcagaa cggaagagac 2460

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cugaucgaaa caaacggaga aacaggagaa aucgucggg acaagggaag agacuucga 3240

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agcccgaaga agaagagaaa ggucgacagc gga 4173

<210> 231

<211> 17

<212> ADN

<213> Secuencia artificial

<220>

<223> Sintético: Promotor T7

<400> 231

taatacgact cactata

17

<210> 232

<211> 50

<212> ADN

<213> Homo sapiens

<220>

<221> misc_característica

<222> (1)..(50)

<223> Beta-globina humana 5 UTR

<400> 232

acatttgctt ctgacacaac tgtgttcact agcaacctca aacagacacc

50

<210> 233

<211> 132

<212> ADN

<213> Homo sapiens

<220>

<221> misc_característica

<222> (1)..(132)

<223> Beta-globina humana 3 UTR

<400> 233

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taaactgggg gatattatga agggccttga gcatctggat tctgcctaataaaaaacatt 120

tattttcatt 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

cataaacctt ggcgcgctcg cggcccgga ctcttctggt cccacagac tcagagagaa 60

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

gctggagcct cggcggcat gcttcttgc cctgggcct ccccccagc cctcctccc 60

ttcctgcacc cgtacccccg tggctttga ataaagtctg agtgggcggc 110

<210> 236

<211> 29

<212> ADN

<213> Xenopus laevis

<220>

<221> misc_característica

<222> (1)..(29)

<223> beta-globina 5 UTR de Xenopus laevis

<400> 236

aagctcagaa taaacgctca actttggcc 29

<210> 237

<211> 130

<212> ADN

<213> Xenopus laevis

<220>

<221> misc_característica

<222> (1)..(130)

<223> beta-globina 3' UTR de Xenopus laevis

<400> 237

accagcctca agaacacccg aatggagtct ctaagctaca taataccaac ttacacttta 60

caaaatgttg tcccccaaaa ttaggccatt cgtatctgct cctaataaaa agaaagtffc 120

ttcacattct 130

<210> 238

<211> 27

<212> ADN

<213> Bos taurus

<220>

<221> misc_característica

<222> (1)..(27)

<223> Hormona de crecimiento bovina 5 UTR

<400> 238

cagggctctg tggacagctc accagct 27

<210> 239

<211> 102

<212> ADN

<213> Bos taurus

<220>

<221> misc_característica

<222> (1)..(102)

<223> Hormona de crecimiento bovina 3 UTR

<400> 239

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tcccactgtc 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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ctcttggtct ttgaataaag cctgagtagg aag

93

<210> 241

<211> 61

<212> ADN

<213> Secuencia artificial

<220>

<223> Sintético: HSD17B4 5 UTR

<400> 241

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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>

<221> base_modificada

<222> (1)..(3)

<223> Enlace PS, nucleótido 2'-O-Me

<220>

<221> base_modificada

<222> (29)..(40)

<223> nucleótido 2'-O-Me

<220>

<221> base_modificada

<222> (69)..(96)

<223> nucleótido 2'-O-Me

<220>

<221> base_modificada

<222> (97)..(100)

<223> Enlace PS, nucleótido 2'-O-Me

<400> 242

uuacagccac gucuacagca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 243

<400> 243

000

<210> 244

<211> 4405

<212> ADN

<213> Secuencia artificial

<220>

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

<400> 244

gggtcccga gtcggcgcc agcggctctg cttgttcgtg tgtgtgtcgt tgcaggcctt 60

attcgatcc atggacaaga agtacagcat cggactggac atcggaacaa acagcgtcgg 120

atgggcagtc atcacagacg aatacaaggt cccgagcaag aagttcaagg tcctgggaaa 180

cacagacaga cacagcatca agaagaacct gatcggagca ctgctgttcg acagcggaga 240

aacagcagaa gcaacaagac tgaagagaac agcaagaaga agatacaca gaagaaagaa 300

cagaatctgc tacctgcagg aaatcttcag caacgaaatg gcaaaggtcg acgacagctt 360

ctccacaga ctggaagaaa gcttcctggt cgaagaagac aagaagcacg aaagacacc 420

gatcttcgga aacatcgtcg acgaagtcgc ataccacgaa aagtaccga caatctacca 480

cctgagaaag aagctggtcg acagcacaga caaggcagac ctgagactga tctacctggc 540

actggcacac atgatcaagt tcagaggaca cttcctgatc gaaggagacc tgaacccgga 600

caacagcgac gtcgacaagc tggtcatcca gctgtccag acatacaacc agctgttcga 660

agaaaacccg atcaacgcaa gcggagtcga cgcaaaggca atcctgagcg caagactgag 720

caagagcaga agactggaaa acctgatcgc acagtgccg ggagaaaaga agaacggact 780

gttcggaaac ctgatcgac tgagcctggg actgacaccg aacttcaaga gcaacttcga 840

cctggcagaa gacgcaaagc tgcagctgag caaggacaca tacgacgacg acctggacaa 900

cctgctggca cagatcggag accagtacgc agacctgttc ctggcagcaa agaacctgag 960

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actggtcaga cagcagctgc cggaaaagta caaggaaatc ttctcgacc agagcaagaa 1140

cggatacgca ggatacatcg acggaggagc aagccaggaa gaattctaca agttcatcaa 1200

gccgatcctg gaaaagatgg acggaacaga agaactgctg gtcaagctga acagagaaga 1260

cctgctgaga aagcagagaa cattcgacaa cggaagcatc ccgcaccaga tccacctggg 1320

agaactgcac gcaatcctga gaagacagga agacttctac ccgttcctga aggacaacag 1380

agaaaagatc gaaaagatcc tgacattcag aatcccgtac tacgtcggac cgctggcaag 1440

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cttcgaagaa gtcgtcgaca agggagcaag cgacagagc ttcatcgaaa gaatgacaaa 1560

cttcgacaag aacctgccga acgaaaaggt cctgccgaag cacagcctgc tgtacgaata 1620

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cgtcgaaatc agcggagtcg aagacagatt caacgcaagc ctgggaacat accacgacct 1860

gctgaagatc atcaaggaca aggacttcct ggacaacgaa gaaaacgaag acatcctgga 1920

agacatcgct ctgacactga cactgttcga agacagagaa atgatcgaag aaagactgaa 1980

gacatacgca cacctgttcg acgacaaggt catgaagcag ctgaagagaa gaagatacac 2040

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aaacatcgct atcgaaatgg caagagaaaa ccagacaaca cagaagggaac agaagaacag 2400

cagagaaaga atgaagagaa tcgaagaagg aatcaaggaa ctgggaagcc agatcctgaa 2460

ggaacacccg gtcgaaaaca cacagctgca gaacgaaaag ctgtacctgt actacctgca 2520

gaacggaaga gacatgtacg tcgaccagga actggacatc aacagactga gcgactacga 2580

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cagaatgaac acaaagtacg acgaaaacga caagctgac agagaagtca aggtcatcac 2940

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aatcaacaac taccaccacg cacacgacgc atacctgaac gcagtcgtcg gaacagcact 3060

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<210> 245

<211> 4188

<212> ADN

<213> Secuencia artificial

<220>

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

<400> 245

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cacagcatca agaagaatct catcggagcc ctgctgtttg actccggcga aaccgcagaa 180

gcgacccggc tcaaacttac cgcgaggcga cgctacaccc ggcggaagaa tcgcatctgc 240

tatctgcaag aaatcttttc gaacgaaatg gcaaagggtg acgacagctt cttccaccgc 300

ctggaagaat ctttctggt ggaggaggac aagaagcatg aacggcatcc tatctttgga 360

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aagttggtg actcaactga caaggccgac ctgagattga tctacttggc cctcgcccat 480

atgatcaaat tccgcggaca cttctgatc gaaggcgatc tgaaccctga taactccgac 540

gtggataagc tgttcattca actggtgcag acctacaacc aactgttcga agaaaacca 600

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c g c c t c g a a a a c c t g a t c g c a c a g t g c c g g g a g a g a a g a a c a c g g a c t t t c g g c a a c 720

t t g a t c g t c t c t c a c t g g g a c t c a c t c c c a a t t c a a g t c c a a t t t t g a c c t g g c c g a g 780

g a c g c g a a g c t g c a a c t c t c a a g g a c a c c t a c g a c g a c g a c t t g g a c a a t t t g t g g c a 840

c a a a t t g g c g a t c a g t a c g c g g a t c t g t t c c t t g c c g c t a g a a c c t t t c g g a c g a a t c 900

t t g t g t c c g a t a t c c t g c g c g t g a a c c g a a a a t a a c c a a g c g c c g c t t a g c g c c t c g 960

a t g a t t a a g c g g t a c g a c g a g c a t c a c c a g g a t c t c a c g c t g c t c a a a g c g c t c g t g a g a 1020

c a g c a a c t g c c t g a a a a g t a c a a g g a g a t t t t c t c g a c c a g t c c a a g a a t g g g t a c g c a 1080

g g g t a c a t c g a t g g a g g c g c c a g c c a g g a a g a g t t c t a t a a g t t c a t c a a g c c a a t c c t g 1140

g a a a a g a t g g a c g g a a c c g a g a a c t g c t g t c a a g t g a a c a g g g a g g a t c t g t c c g c 1200

a a a c a g a g a a c c t t t g a c a a c g g a a g c a t t c c a c a c c a g a t c c a t c t g g g t g a g t g c a c 1260

g c c a t c t t g c g g c g c c a g g a g g a c t t t t a c c a t t c c t c a a g g a c a a c c g g g a a a g a t c 1320

g a g a a a a t t c t g a c g t t c c g c a t c c c g t a t t a c t g g g g c c a c t g g c g c g c g g c a a t t c g 1380

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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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gaagatcaat agcttattca tctcttttc ttttcgttg gtgtaaagcc aacaccctgt 4380

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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 catcgagacc ctgctgttg actccggcga 240

aaccgcagaa gcgacccggc tcaaactac cgcgaggcga cgctacacc gccggaagaa 300

tcgcatctgc tatctgcaag aaatctttc gaacgaaatg gcaaaggagg acgacagctt 360

ctccaccgc ctggaagaat ctttctggt ggaggaggac aagaagcatg aacggcatcc 420

tatctttgga aacatcgtgg acgaagtggc gtaccacgaa aagtaccga ccatctacca 480

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cctcgcccat atgatcaaat tccgcggaca cttctgac gaaggcgac tgaaccctga 600

taactccgac gtggataagc tggtcattca actggtgcag acctacaacc aactgttcga 660

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gaagtgcgg cgctcgaaa acctgatcgc acagctgccg ggagagaaga agaacggact 780

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cctgaaaagc aaacttgtgt cggactttcg gaaggacttt cagttttaca aagtgagaga 3000

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caggaagagg cactgatcg aaactaacgg agaaacgggc gaaatcgtgt gggacaaggg 3300

cagggacttc gcaactgttc gcaaagtgt ctctatgccg caagtcaata ttgtgaagaa 3360

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caagctcatt gcacgcaaga aagactggga cccgaagaag tacggaggat tcgattcgcc 3480

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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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attcggtacc gccaccatgc ctaagaaaaa gcggaaggctc gacggggata agaagtactc 120

aatcgggctg gatatcggaa ctaattccgt gggttgggca gtgatcacgg atgaatacaa 180

agtgccgtcc aagaagtta aggtcctggg gaacaccgat agacacagca tcaagaaaaa 240

tctcatcgga gccctgctgt ttgactccgg cgaaaccgca gaagcgaccc ggctcaaacg 300

taccgcgagg cgacgtaca cccggcggaa gaatcgcatc tgctatctgc aagagatctt 360

ttcgaacgaa atggcaaagg tcgacgacag cttcttcac cgcttgaag aatctttcct 420

ggtgaggag gacaagaagc atgaacggca tcctatcttt gaaacatcg tcgacgaagt 480

ggcgtaccac gaaaagtacc cgaccatcta ccatctcgg aagaagttgg ttgactcaac 540

tgacaaggcc gacctcagat tgatctactt ggccctcgcc catatgatca aattccgcgg 600

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tcaactgggtg cagacctaca accaactgtt cgaagaaaac ccaatcaatg ctagcggcgt 720

cgatgccaag gccatcctgt ccgccgggt gtcgaagtcg cggcgctcg aaaacctgat 780

cgcacagctg ccgggagaga aaaagaacgg acttttcggc aacttgatcg ctctctcact 840

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ccttgacaac gaggagaacg aggacatcct ggaagatata gtcctgacct tgaccctttt 1980

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gaaagaaaat gaagatcaat agcttattca tctctttttc ttttcgttg gtgtaaagcc 4320

aacaccctgt ctaaaaaaca taaatttctt taatcatttt gcctcttttc tctgtgcttc 4380

aattaataaa aaatggaaag aacctcgag 4409

<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 gcttcttggt cgaagaagac aagaagcagc aaagacaccc gatcttcgga 360

aacatcgtcg acgaagtcgc ataccacgaa aagtaccgga caatctacca cctgagaaag 420

aagctggtcg acagcacaga caaggcagac ctgagactga tctacctggc actggcacac 480

atgatcaagt tcagaggaca cttctgatc gaaggagacc tgaaccgga caacagcgac 540

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agactggaaa acctgatcg acagctgccg ggagaaaaga agaacggact gttcggaac 720

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gaagtcttg acgcaacact gatccaccag agcatcacag gactgtacga aacaagaatc 4080

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<210> 251

<211> 4411

<212> ADN

<213> Secuencia artificial

<220>

<223> Sintético: transcrito de Cas9 con 5 UTR de HSD, ORF correspondiente a la
SEQ ID NO: 250, secuencia de Kozak, y 3 UTR de ALB

<400> 251

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<210> 252

<211> 4140

<212> ADN

<213> Secuencia artificial

<220>

<223> Sintético: ORF de Cas9 con codones de mínima uridina de uso frecuente en humanos
en general; 12.75 % de contenido de U

<400> 252

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cacagcatca agaagaacct gatcggcgcc ctgctgttcg acagcggcga gaccgccgag 180

gccaccagac tgaagagaac cgccagaaga agatacacca gaagaaagaa cagaatctgc 240

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<210> 253

<211> 4411

<212> ADN

<213> Secuencia artificial

<220>

<223> Sintético: transcrito de Cas9 con 5 UTR de HSD, ORF correspondiente a la

SEQ ID NO: 252, secuencia de Kozak, y 3 UTR de ALB

<400> 253

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<210> 254

<211> 4140

<212> ADN

<213> Secuencia artificial

<220>

<223> Sintético: ORF de Cas9 con codones de mínima uridina usados con poca frecuencia
en humanos en general; 12.75 % de contenido de U

<400> 254

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tacagcgtag tagtagtagc gaaagtagaa aaagggaaaa gcaaaaaact aaaaagcgta 3480

aaagaactac tagggataac gataatggaa cgaagcagct tcgaaaaaaa cccgatagac 3540

ttcctagaag cgaaagggtg caaagaagta aaaaaagacc taataataaa actaccgaaa 3600

tacagcctat tcgaactaga aaacgggcga aaacgaatgc tagcgagcgc gggggaacta 3660

caaaaaggga acgaactagc gctaccgagc aaatacgtaa acttcctata cctagcgagc 3720

cactacgaaa aactaaaagg gagcccgga gacaacgaac aaaaacaact attcgtagaa 3780

caacacaaac actacctaga cgaaataata gaacaaataa gcgaattcag caaacgagta 3840

atactagcgg acgcgaacct agacaaagta ctaagcgcgt acaacaaaca ccgagacaaa 3900

ccgatacgag aacaagcgga aacataata cacctattca cgtaacgaa cctagggcg 3960

ccggcggcgt tcaaatactt cgacacgacg atagaccgaa aacgatacac gagcacgaaa 4020

gaagtactag acgcgacgct aatacaccaa agcataacgg ggctatacga aacgcgaata 4080

gacctaagcc aactaggggg ggacgggggg gggagcccga aaaaaaacg aaaagtatga 4140

<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

<400> 255

gggtcccga gtcggcgtcc agcggctctg cttgttcgtg tgtgtgtcgt tgcaggcctt 60

attcgatcc gccacatgg acaaaaaata cagcataggg ctagacatag ggacgaacag 120

cgtagggtgg gcgtaataa cggacgaata caaagtaccg agcaaaaaat tcaaagtact 180

agggaacacg gaccgacaca gcataaaaaa aaacctaata ggggcgctac tattcgacag 240

cggggaaacg gcggaagcga cgcgactaaa acgaacggcg cgacgacgat acacgcgacg 300

aaaaaaccga atatgctacc tacaagaaat attcagcaac gaaatggcga aagtagacga	360
cagcttcttc caccgactag aagaaagctt cctagtagaa gaagacaaaa aacacgaacg	420
acacccgata ttcgggaaca tagtagacga agtagcgtag cacgaaaaat acccgacgat	480
ataccaccta cgaaaaaac tagtagacag cacggacaaa gcggacctac gactaatata	540
cctagcgcta gcgcacatga taaaattccg agggcacttc ctaatagaag gggacctaaa	600
cccggacaac agcgacgtag acaactatt catacaacta gtacaaacgt acaaccaact	660
attcgaagaa aacccgataa acgcgagcgg ggtagacgcg aaagcgatac taagcgcgcg	720
actaagcaaa agccgacgac tagaaaacct aatagcgcaa ctaccggggg aaaaaaaaaa	780
cgggctattc gggaacctaa tagcgctaag cctagggcta acgccgaact tcaaaagcaa	840
cttcgaccta gcggaagacg cgaaactaca actaagcaaa gacacgtacg acgacgacct	900
agacaaccta ctacgcaaa taggggacca atacgcggac ctattcctag cggcgaaaaa	960
cctaagcgac gcgatactac taagcgacat actacgagta aacacggaaa taacgaaagc	1020
gccgctaagc gcgagcatga taaacgata cgacgaacac caccaagacc taacgtact	1080
aaaagcgcta gtacgacaac aactaccgga aaaatacaaa gaaatattct tcgaccaaag	1140

caaaaacggg tacgcggggt acatagacgg gggggcgagc caagaagaat tctacaaatt 1200

cataaaaccg atactagaaa aaatggacgg gacggaagaa ctactagtaa aactaaaccg 1260

agaagaccta ctacgaaaac aacgaacgtt cgacaacggg agcataccgc accaaataca 1320

cctaggggaa ctacacgca tactacgacg acaagaagac ttctaccgt tcctaaaaga 1380

caaccgagaa aaaatagaaa aaatactaac gttccgaata ccgtactacg tagggccgct 1440

agcgcgaggg aacagccgat tcgcgtggat gacgcgaaaa agcgaagaaa cgataacgcc 1500

gtggaacttc gaagaagtag tagacaaagg ggcgagcgcg caaagcttca tagaacgaat 1560

gacgaacttc gacaaaaacc taccgaacga aaaagtacta ccgaaacaca gcctactata 1620

cgaatacttc acggtataca acgaactaac gaaagtaaaa tacgtaacgg aagggatgcg 1680

aaaaccggcg ttctaagcg gggaacaaaa aaaagcgata gtagacctac tattcaaac 1740

gaaccgaaaa gtaacggtaa aacaactaaa agaagactac ttcaaaaaaa tagaatgctt 1800

cgacagcgta gaaataagcg gggtagaaga ccgattcaac gcgagcctag ggacgtacca 1860

cgacctacta aaaataataa aagacaaaga cttcctagac aacgaagaaa acgaagacat 1920

actagaagac atagtactaa cgctaacgct attcgaagac cgagaaatga tagaagaacg 1980

actaaaaacg tacgcgcacc tattcgacga caaagtaatg aaacaactaa aacgacgacg 2040

atacacgggg tgggggacgac taagccgaaa actaataaac gggatacgag acaaacaag 2100

cgggaaaacg atactagact tcctaaaaag cgacgggttc gcgaaccgaa acttcatgca 2160

actaatacac gacgacagcc taacgttcaa agaagacata caaaaagcgc aagtaagcgg 2220

gcaaggggac agcctacacg aacacatagc gaacctagcg gggagcccgg cgataaaaaa 2280

agggatacta caaacggtaa aagtagtaga cgaactagta aaagtaatgg ggcgacacaa 2340

accggaaaac atagtaatag aaatggcgcg agaaaaccaa acgacgcaa aaggcgaaaa 2400

aaacagccga gaacgaatga aacgaataga agaagggata aaagaactag ggagccaaat 2460

actaaaagaa caccggtag aaaacacgca actacaaaac gaaaaactat acctatacta 2520

cctacaaaac gggcgagaca tgtacgtaga ccaagaacta gacataaacc gactaagcga 2580

ctacgacgta gaccacatag taccgcaaag cttcctaaaa gacgacagca tagacaacaa 2640

agtactaacg cgaagcgaca aaaaccgagg gaaaagcgac aacgtaccga gcgaagaagt 2700

agtaaaaaaa atgaaaaact actggcgaca actactaaac gcgaaactaa taacgcaacg 2760

aaaattcgac aacctaacga aagcggaacg aggggggcta agcgaactag acaaagcggg 2820

gttcataaaa cgacaactag tagaaacgcg acaataacg aaacacgtag cgcaaatact 2880

agacagccga atgaacacga aatacgacga aaacgacaaa ctaatacgag aagtaaaagt 2940

aataacgcta aaaagcaaac tagtaagcga cttccgaaaa gacttccaat tctacaaagt 3000

acgagaaata aacaactacc accacgcgca cgacgcgtac ctaaacgcgg tagtagggac 3060

ggcgctaata aaaaaatacc cgaaactaga aagcgaattc gtatacgggg actacaaagt 3120

atacgacgta cgaaaaatga tagcgaaaag cgaacaagaa ataggggaaag cgacggcgaa 3180

atacttcttc tacagcaaca taatgaactt cttcaaaacg gaaataacgc tagcgaacgg 3240

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caaagggcga gacttcgcga cggtacgaaa agtactaagc atgccgcaag taaacatagt 3360

aaaaaaaaacg gaagtacaaa cggggggggtt cagcaaagaa agcatactac cgaaacgaaa 3420

cagcgacaaa ctaatagcgc gaaaaaaga ctgggacccg aaaaaatacg gggggttcga 3480

cagcccgacg gtagcgtaca gcgtactagt agtagcgaaa gtagaaaaag ggaaaagcaa 3540

aaaactaaaa agcgtaaaag aactactagg gataacgata atggaacgaa gcagcttcga 3600

aaaaaaccg atagacttcc tagaagcgaa aggtacaaa gaagtaaaaa aagacctaata 3660

aataaaaacta ccgaaatata gcctattcga actagaaaac gggcgaaaac gaatgctagc 3720

gagcggggg gaactacaaa aagggaacga actagcgcta ccgagcaaata acgtaaactt 3780

cctataccta gcgagccact acgaaaaact aaaagggagc ccggaagaca acgaacaaaa 3840

acaactattc gtagaacaac acaaacta cctagacgaa ataatagaac aaataagcga 3900

attcagcaaa cgagtaatac tagcggacgc gaacctagac aaagtactaa gcgcgtacaa 3960

caaacaccga gacaaaccga tacgagaaca agcggaaaac ataatacacc tattcacgct 4020

aacgaaccta ggggcgccgg cggcgttcaa atacttcgac acgacgatag accgaaaacg 4080

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atacgaaacg cgaatagacc taagccaact agggggggac ggggggggga gcccgaaaaa 4200

aaaacgaaaa gtatgactag ccatcacatt taaaagcatc tcagcctacc atgagaataa 4260

gagaaagaaa atgaagatca atagcttatt catctctttt tcttttcgt tgggtgtaaag 4320

ccaacaccct gtctaaaaaa cataaatttc ttaatcatt ttgcctcttt tctctgtgct 4380

tcaattaata aaaaatggaa agaacctcga g 4411

<210> 256

<211> 4411

<212> ADN

<213> Secuencia artificial

<220>

<223> Sintético: transcrito de Cas9 con AGG como los primeros tres nucleótidos para el uso con CleanCap™, 5 UTR de HSD, ORF correspondiente a la SEQ ID NO: 204, Secuencia de Kozak, y 3 UTR de ALB

<400> 256

agggtcccga gtcggcgtcc agcggctctg cttgttcgtg tgtgtgtcgt tgcaggcctt 60

attcggatcc gccacccatgg acaagaagta cagcatcgga ctggacatcg gaacaaacag 120

cgtcggatgg gcagtcacga cagacgaata caaggtcccg agcaagaagt tcaaggtcct 180

gggaaacaca gacagacaca gcatcaagaa gaacctgac ggagcactgc ttttcgacag 240

cggagaaaca gcagaagcaa caagactgaa gagaacagca agaagaagat acacaagaag 300

aaagaacaga atctgctacc tgcaggaaat cttcagcaac gaaatggcaa aggtcgacga 360

cagcttcttc cacagactgg aagaaagctt cctggtcgaa gaagacaaga agcacgaaag 420

acacccgatc ttcggaaaca tcgtcgacga agtcgcatac cacgaaaagt acccgacaat 480

ctaccacctg agaaagaagc tggtcgacag cacagacaag gcagacctga gactgatcta 540

cctggcactg gcacacatga tcaagttcag aggacacttc ctgatcgaag gagacctgaa 600

cccggacaac agcgacgtcg acaagctgtt catccagctg gtccagacat acaaccagct 660

gttcgaagaa aacccgatca acgcaagcgg agtcgacgca aaggcaatcc tgagcgcaag 720

actgagcaag agcagaagac tggaaaacct gatcgcacag ctgccgggag aaaagaagaa 780

cggactgttc ggaaacctga tcgactgag cctgggactg acaccgaact tcaagagcaa 840

cttcgacctg gcagaagacg caaagctgca gctgagcaag gacacatacg acgacgacct 900

ggacaacctg ctggcacaga tcggagacca gtacgcagac ctgttcctgg cagcaaagaa 960

cctgagcgac gcaatcctgc tgagcgacat cctgagagtc aacacagaaa tcacaaaggc 1020

accgctgagc gcaagcatga tcaagagata cgacgaacac caccaggacc tgacactgct 1080

gaaggcactg gtcagacagc agtgccgga aaagtacaag gaaatcttct tcgaccagag 1140

caagaacgga tacgcaggat acatcgacgg aggagcaagc caggaagaat tctacaagtt 1200

catcaagccg atcctggaaa agatggacgg aacagaagaa ctgctgggtca agctgaacag 1260

agaagacctg ctgagaaaagc agagaacatt cgacaacgga agcatcccg accagatcca 1320

cctgggagaa ctgcacgcaa tcctgagaag acaggaagac ttctaccgt 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 ttcctgagcg gagaacagaa gaaggcaatc gtcgacctgc tgttcaagac 1740

aaacagaaag gtcacagtca agcagctgaa ggaagactac ttcaagaaga tcgaatgctt 1800

cgacagcgtc gaaatcagcg gagtcgaaga cagattcaac gcaagcctgg gaacatacca 1860

cgacctgctg aagatcatca aggacaagga cttctggac aacgaagaaa acgaagacat 1920

cctggaagac atcgtcctga cactgacact gttcgaagac agagaaatga tcgaagaaag 1980

actgaagaca tacgcacacc tgttcgacga caaggtcatg aagcagctga agagaagaag 2040

atacacagga tggggaagac tgagcagaaa gctgatcaac ggaatcagag acaagcagag 2100

cggaaagaca atcctggact tcctgaagag cgacggattc gcaaacagaa acttcatgca 2160

gctgatccac gacgacagcc tgacattcaa ggaagacatc cagaaggcac aggtcagcgg 2220

acaggagagac agcctgcacg aacacatcgc aaacctggca ggaagcccgg caatcaagaa 2280

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gccggaaaac atcgtcatcg aaatggcaag agaaaaccag acaacacaga agggacagaa 2400

gaacagcaga gaaagaatga agagaatcga agaaggaatc aaggaactgg gaagccagat 2460

cctgaaggaa cacccggtcg aaaacacaca gctgcagaac gaaaagctgt acctgtacta 2520

cctgcagaac ggaagagaca tgtacgtcga ccaggaactg gacatcaaca gactgagcga 2580

ctacgacgtc gaccacatcg tcccgcagag cttcctgaag gacgacagca tcgacaacaa 2640

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aaagttcgac aacctgacaa aggcagagag aggaggactg agcgaactgg acaaggcagg 2820

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catcacactg aagagcaagc tggtcagcga cttcagaaag gacttccagt tctacaaggt 3000

cagagaaatc aacaactacc accacgcaca cgacgcatac ctgaacgcag tcgtcggaac 3060

agcactgac aagaagtacc cgaagctgga aagcgaattc gtctacggag actacaaggt 3120

ctacgacgtc agaaagatga tcgcaaagag cgaacaggaa atcggaaaagg caacagcaaa 3180

gtacttcttc tacagcaaca tcatgaactt cttcaagaca gaaatcacac tggcaaacgg 3240

agaaatcaga aagagaccgc tgatcgaaac aaacggagaa acaggagaaa tcgtctggga 3300

caagggaaga gacttcgcaa cagtcagaaa ggtcctgagc atgccgcagg tcaacatcgt 3360

caagaagaca gaagtccaga caggaggatt cagcaaggaa agcatcctgc cgaagagaaa 3420

cagcgacaag ctgatcgcaa gaaagaagga ctgggacccg aagaagtacg gaggattcga 3480

cagcccgaca gtcgcataca gcgtcctggt cgtcgcaaag gtcgaaaagg gaaagagcaa 3540

gaagctgaag agcgtcaagg aactgctggg aatcacaatc atggaaagaa gcagcttcga 3600

aaagaacccg atcgacttcc tggaagcaaa gggatacaag gaagtcaaga aggacctgat 3660

catcaagctg ccgaagtaca gcctgttcga actggaaaac ggaagaaaga gaatgctggc 3720

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gcagctgttc gtcgaacagc acaagcacta cctggacgaa atcatcgaac agatcagcga 3900

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gacaaacctg ggagcaccgg cagcattcaa gtacttcgac acaacaatcg acagaaagag 4080

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gtacgaaaca agaatcgacc tgagccagct gggaggagac ggaggaggaa gcccgaagaa 4200

gaagagaaag gtctagctag 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> 257

<211> 4481

<212> ADN

<213> Secuencia artificial

<220>

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

<400> 257

gggcagatcg cctggagacg ccatccacgc tgttttgacc tccatagaag acaccgggac 60

cgatccagcc tccgcggccg ggaacggtgc attggaacgc ggattccccg tgccaagagt 120

gactcaccgt ccttgacacg gccacatgg acaagaagta cagcatcgga ctggacatcg 180

gaacaaacag cgtcggatgg gcagtcatca cagacgaata caagggtccc agcaagaagt 240

tcaaggtcct gggaacaca gacagacaca gcatcaagaa gaacctgatc ggagcactgc 300

tggtcgacag cggagaaaca gcagaagcaa caagactgaa gagaacagca agaagaagat 360

acacaagaag aaagaacaga atctgctacc tgcaggaaat cttcagcaac gaaatggcaa 420

aggtcgacga cagcttcttc cacagactgg aagaaagctt cctggtcgaa gaagacaaga 480

agcacgaaag acacccgatc ttcggaaaca tcgtcgacga agtcgcatac cacgaaaagt 540

acccgacaat ctaccacctg agaaagaagc tggtcgacag cacagacaag gcagacctga 600

gactgatcta cctggcactg gcacacatga tcaagttcag aggacacttc ctgatcgaag 660

gagacctgaa cccggacaac agcgacgtcg acaagctgtt catccagctg gtccagacat 720

acaaccagct gttcgaagaa aaccgatca acgcaagcgg agtcgacgca aaggcaatcc 780

tgagcgcaag actgagcaag agcagaagac tggaaaacct gatcgcacag ctgccgggag 840

aaaagaagaa cggactgttc ggaaacctga tcgcactgag cctgggactg acaccgaact 900

tcaagagcaa cttcgacctg gcagaagacg caaagctgca gctgagcaag gacacatacg 960

acgacgacct ggacaacctg ctggcacaga tcggagacca gtacgcagac ctgttcctgg 1020

cagcaaagaa cctgagcgac gcaatcctgc tgagcgacat cctgagagtc aacacagaaa 1080

tcacaaaggc accgctgagc gcaagcatga tcaagagata cgacgaacac caccaggacc 1140

tgacactgct gaaggcactg gtcagacagc agctgccgga aaagtacaag gaaatcttct 1200

tcgaccagag caagaacgga tacgcaggat acatcgacgg aggagcaagc caggaagaat 1260

tctacaagtt catcaagccg atcctggaaa agatggacgg aacagaagaa ctgctggtca 1320

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accagatcca cctgggagaa ctgcacgcaa tcctgagaag acaggaagac ttctaccgt 1440

tcctgaagga caacagagaa aagatcgaaa agatcctgac attcagaatc ccgtactacg 1500

tcggaccgct ggcaagagga aacagcagat tcgcatggat gacaagaaag agcgaagaaa 1560

caatcacacc gtggaacttc gaagaagtcg tcgacaaggg agcaagcgca cagagcttca 1620

tcgaaagaat gacaaacttc gacaagaacc tgccgaacga aaaggtcctg ccgaagcaca 1680

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tgttcaagac aaacagaaag gtcacagtca agcagctgaa ggaagactac ttcaagaaga 1860

tcgaatgctt cgacagcgtc gaaatcagcg gagtgaaga cagattcaac gcaagcctgg 1920

gaacatacca cgacctgtg aagatcatca aggacaagga cttcctggac aacgaagaaa 1980

acgaagacat cctggaagac atcgtcctga cactgacact gttcgaagac agagaaatga 2040

tcgaagaaag actgaagaca tacgcacacc tgttcgacga caaggtcatg aagcagctga 2100

agagaagaag atacacagga tggggaagac tgagcagaaa gctgatcaac ggaatcagag 2160

acaagcagag cggaagaca atcctggact tcctgaagag cgacggattc gcaaacagaa 2220

acttcatgca gctgatccac gacgacagcc tgacattcaa ggaagacatc cagaaggcac 2280

aggtcagcgg acaggagac agcctgcacg aacacatcg aaacctggca ggaagcccgg 2340

caatcaagaa gggaatcctg cagacagtca aggtcgtcga cgaactggc aaggtcatgg 2400

gaagacacaa gccgaaaac atcgtcatcg aaatggcaag agaaaaccag acaacacaga 2460

agggacagaa gaacagcaga gaaagaatga agagaatcga agaaggaatc aaggaactgg 2520

gaagccagat cctgaaggaa caccggctcg aaaacacaca gctgcagaac gaaaagctgt 2580

acctgtacta cctgcagaac ggaagagaca tgtacgtcga ccaggaactg gacatcaaca 2640

gactgagcga ctacgacgtc gaccacatcg tcccgcagag cttcctgaag gacgacagca 2700

tcgacaacaa ggtcctgaca agaagcgaca agaacagagg aaagagcgac aacgtcccga 2760

gcgaagaagt cgtaagaag atgaagaact actggagaca gctgctgaac gcaaagctga 2820

tcacacagag aaagtctgac aacctgacaa aggcagagag aggaggactg agcgaactgg 2880

acaaggcagg attcatcaag agacagctgg tcgaaacaag acagatcaca aagcacgtcg 2940

cacagatcct ggacagcaga atgaacacaa agtacgacga aaacgacaag ctgatcagag 3000

aagtcaaggt catcacactg aagagcaagc tggtcagcga cttcagaaag gacttccagt 3060

tctacaaggt cagagaaatc aacaactacc accacgcaca cgacgcatac ctgaacgcag 3120

tcgtcggaac agcactgatc aagaagtacc cgaagctgga aagcgaattc gtctacggag 3180

actacaaggt ctacgacgtc agaaagatga tcgcaaagag cgaacaggaa atcgaaagg 3240

caacagcaaa gtacttcttc tacagcaaca tcatgaactt cttcaagaca gaaatcacac 3300

tggcaaacgg agaaatcaga aagagaccgc tgatcgaaac aaacggagaa acaggagaaa 3360

tcgtctggga caaggaaga gacttcgcaa cagtcagaaa ggtcctgagc atgccgcagg 3420

tcaacatcgt caagaagaca gaagtccaga caggaggatt cagcaaggaa agcatcctgc 3480

cgaagagaaa cagcgacaag ctgatcgcaa gaaagaagga ctgggaccgc aagaagtacg 3540

gaggattcga cagcccgaca gtcgcataca gcgtcctggt cgtcgcaaag gtcgaaaagg 3600

gaaagagcaa gaagctgaag agcgtcaagg aactgctggg aatcacaatc atggaaagaa 3660

gcagcttcga aaagaacccg atcgacttcc tggaagcaaa gggatacaag gaagtcaaga 3720

aggacctgat catcaagctg ccgaagtaca gcctgttcga actggaaaac ggaagaaaga 3780

gaatgctggc aagcgcagga gaactgcaga agggaaacga actggcactg ccgagcaagt 3840

acgtcaactt cctgtacctg gcaagccact acgaaaagct gaagggaagc ccggaagaca 3900

acgaacagaa gcagctgttc gtcgaacagc acaagcacta cctggacgaa atcatcgaac 3960

agatcagcga attcagcaag agagtcatcc tggcagacgc aaacctggac aaggtcctga 4020

gcgcatacaa caagcacaga gacaagccga tcagagaaca ggcagaaaac atcatccacc 4080

tgttcacact gacaaacctg ggagcaccgg cagcattcaa gtacttcgac acaacaatcg 4140

acagaaagag atacacaagc acaaaggaag tcctggacgc aacctgatc caccagagca 4200

tcacaggact gtacgaaaca agaatcgacc tgagccagct gggaggagac ggaggaggaa 4260

gcccgaagaa gaagagaaaag gtctagctag ccatcacatt taaaagcatc tcagcctacc 4320

atgagaataa gagaaagaaa atgaagatca atagcttatt catctctttt tcttttcgt 4380

tggtgtaaag ccaacaccct gtctaaaaaa cataaatttc ttaatcatt ttgcctcttt 4440

tctctgtgct tcaattaata aaaaatggaa agaacctga g 4481

<210> 258

<211> 4348

<212> ADN

<213> Secuencia artificial

<220>

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

<400> 258

gggacatttg cttctgacac aactgtgttc actagcaacc tcaaacagac accggatctg 60

ccaccatgga caagaagtac agcatcggac tggacatcgg aacaacagc gtcggatggg 120

cagtcacac agacgaatac aaggtccga gcaagaagtt caaggtcctg ggaaacacag 180

acagacacag catcaagaag aacctgatcg gagcactgct gtcgacagc ggagaaacag 240

cagaagcaac aagactgaag agaacagcaa gaagaagata cacaagaaga aagaacagaa 300

tctgtacct gcaggaaatc ttcagcaacg aaatggcaaa ggtcgacgac agcttcttcc 360

acagactgga agaaagcttc ctggtcgaag aagacaagaa gcacgaaaga caccgatct 420

tcggaaacat cgtcgacgaa gtcgcatacc acgaaaagta cccgacaatc taccacctga 480

gaaagaagct ggtcgacagc acagacaagg cagacctgag actgatctac ctggcactgg 540

cacacatgat caagttcaga ggacacttcc tgatcgaagg agacctgaac ccggacaaca 600

gcgacgtcga caagctgttc atccagctgg tccagacata caaccagctg ttcgaagaaa 660

acccgatcaa cgcaagcgga gtcgacgcaa aggcaatcct gagcgcaaga ctgagcaaga 720

gcagaagact ggaaaacctg atcgcacagc tgccgggaga aaagaagaac ggactgttcg 780

gaaacctgat cgactgagc ctgggactga caccgaactt caagagcaac ttcgacctgg 840

cagaagacgc aaagctgcag ctgagcaagg acacatacga cgacgacctg gacaacctgc 900

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caagcatgat caagagatac gacgaacacc accaggacct gacctgctg aaggcactgg 1080

tcagacagca gctgccggaa aagtacaagg aaatcttctt cgaccagagc aagaacggat 1140

acgcaggata catcgacgga ggagcaagcc aggaagaatt ctacaagttc atcaagccga 1200

tcctggaaaa gatggacgga acagaagaac tgctggtcaa gctgaacaga gaagacctgc 1260

tgagaaagca gagaacattc gacaacggaa gcatcccgca ccagatccac ctggggagaac 1320

tgcacgcaat cctgagaaga caggaagact tctacccgtt cctgaaggac aacagagaaa 1380

agatcgaaaa gatcctgaca ttcagaatcc cgtactacgt cggaccgctg gcaagaggaa 1440

acagcagatt cgcatggatg acaagaaaga gcgaagaaac aatcacaccg tggaacttcg 1500

aagaagtcgt cgacaaggga gcaagcgcac agagcttcat cgaaagaatg acaaacttcg 1560

acaagaacct gccgaacgaa aaggtcctgc cgaagcacag cctgctgtac gaatacttca 1620

cagtctacaa cgaactgaca aaggtcaagt acgtcacaga aggaatgaga aagccggcat 1680

tcctgagcgg agaacagaag aaggcaatcg tcgacctgct gttcaagaca aacagaaagg 1740

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aaatcagcgg agtcgaagac agattcaacg caagcctggg aacataccac gacctgtga 1860

agatcatcaa ggacaaggac ttctggaca acgaagaaaa cgaagacatc ctggaagaca 1920

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ggggaagact gagcagaaag ctgatcaacg gaatcagaga caagcagagc ggaaagacaa 2100

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agacagtcaa ggtcgtcgac gaactggtca aggtcatggg aagacacaag ccggaaaaca 2340

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aaagaatgaa gagaatcgaa gaaggaatca aggaactggg aagccagatc ctgaaggaac 2460

acccggtcga aaacacacag ctgcagaacg aaaagctgta cctgtactac ctgcagaacg 2520

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accacatcgt cccgcagagc ttcctgaagg acgacagcat cgacaacaag gtcctgacaa 2640

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tgaacacaaa gtacgacgaa aacgacaagc tgatcagaga agtcaaggtc atcacactga 2940

agagcaagct ggtcagcgac ttcagaaagg acttcagtt ctacaaggtc agagaaatca 3000

acaactacca ccacgcacac gacgcatacc tgaacgcagt cgtcggaaca gcactgatca 3060

agaagtaccc gaagctggaa agcgaattcg tctacggaga ctacaaggtc tacgacgtca 3120

gaaagatgat cgaaagagc gaacaggaaa tcggaaaggc aacagcaaag tacttcttct 3180

acagcaacat catgaacttc ttcaagacag aaatcacact ggcaaacgga gaaatcagaa 3240

agagaccgct gatcgaaaca aacggagaaa caggagaaat cgtctgggac aagggaagag 3300

acttcgaac agtcagaaag gtcctgagca tgccgcaggt caacatcgtc aagaagacag 3360

aagtccagac aggaggattc agcaaggaaa gcatcctgcc gaagagaaac agcgacaagc 3420

tgatcgcaag aaagaaggac tgggacccga agaagtacgg aggattcgac agcccgacag 3480

tcgcatacag cgtcctggtc gtcgcaaagg tcgaaaaggg aaagagcaag aagctgaaga 3540

gctgaagga actgctggga atcacaatca tggaaagaag cagcttcgaa aagaaccga 3600

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gaatcgacct gagccagctg ggaggagacg gaggaggaag cccgaagaag aagagaaagg 4200

tctagctagc gctcgctttc ttgctgtcca atttctatta aaggttcctt tgttcctaa 4260

gtccaactac taaactgggg gatattatga agggccttga gcatctggat tctgcctaat 4320

aaaaaacatt tattttcatt gcctcgag 4348

<210> 259

<211> 4325

<212> ADN

<213> Secuencia artificial

<220>

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

<400> 259

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aggtcccgag caagaagttc aaggtcctgg gaaacacaga cagacacagc atcaagaaga 180

acctgatcgg agcactgctg ttcgacagcg gagaacagc agaagcaaca agactgaaga 240

gaacagcaag aagaagatac acaagaagaa agaacagaat ctgctacctg caggaaatct 300

tcagcaacga aatggcaaag gtcgacgaca gcttcttcca cagactggaa gaaagcttcc	360
tggtcgaaga agacaagaag cacgaaagac acccgatctt cggaacatc gtcgacgaag	420
tcgcatacca cgaaaagtac ccgacaatct accacctgag aaagaagctg gtcgacagca	480
cagacaaggc agacctgaga ctgatctacc tggcactggc acacatgatc aagttcagag	540
gacacttctt gatcgaagga gacctgaacc cggacaacag cgacgtcgac aagctgttca	600
tccagctggg ccagacatac aaccagctgt tcgaagaaaa cccgatcaac gcaagcggag	660
tcgacgcaaa ggcaatcctg agcgcaagac tgagcaagag cagaagactg gaaaacctga	720
tcgcacagct gccggggagaa aagaagaacg gactgttcgg aaacctgatc gcactgagcc	780
tgggactgac accgaacttc aagagcaact tcgacctggc agaagacgca aagctgcagc	840
tgagcaagga cacatacgac gacgacctgg acaacctgct ggcacagatc ggagaccagt	900
acgcagacct gttcttgga gcaaagaacc tgagcgacgc aatctgctg agcgacatcc	960
tgagagtcaa cacagaaatc acaaaggcac cgctgagcgc aagcatgatc aagagatacg	1020
acgaacacca ccaggacctg acactgctga aggcactggg cagacagcag ctgccggaaa	1080
agtacaagga aatcttcttc gaccagagca agaacggata cgcaggatac atcgacggag	1140
gagcaagcca ggaagaattc tacaagtca tcaagccgat cctggaaaag atggacggaa	1200

cagaagaact gctggtcaag ctgaacagag aagacctgct gagaaagcag agaacattcg 1260

acaacggaag catcccgcac cagatccacc tgggagaact gcacgcaatc ctgagaagac 1320

aggaagactt ctaccggttc ctgaaggaca acagagaaaa gatcgaaaag atcctgacat 1380

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caagcgaca gagcttcac gaaagaatga caaacttcga caagaacctg ccgaacgaaa 1560

aggtcctgcc gaagcacagc ctgctgtacg aatacttcac agtctacaac gaactgaca 1620

aggtcaagta cgtcacagaa ggaatgagaa agccggcatt cctgagcgga gaacagaaga 1680

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gattcaacgc aagcctggga acataccacg acctgctgaa gatcatcaag gacaaggact 1860

tcctggacaa cgaagaaaac gaagacatcc tggaagacat cgtcctgaca ctgacactgt 1920

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aggtcatgaa gcagctgaag agaagaagat acacaggatg gggaagactg agcagaaaagc 2040

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acggattcgc aaacagaaac ttcatgcagc tgatccacga cgacagcctg acattcaagg 2160

aagacatcca gaaggcacag gtcagcggac agggagacag cctgcacgaa cacatcgaa 2220

acctggcagg aagcccgga atcaagaagg gaatcctgca gacagtcaag gtcgtcgacg 2280

aactggtcaa ggtcatggga agacacaagc cggaatacat cgatcatgaa atggcaagag 2340

aaaaccagac aacacagaag ggacagaaga acagcagaga aagaatgaag agaatcgaag 2400

aaggaatcaa ggaactggga agccagatcc tgaaggaaca cccggtcgaa aacacacagc 2460

tgagaacga aaagctgtac ctgtactacc tgagaacgg aagagacatg tacgtcgacc 2520

aggaactgga catcaacaga ctgagcgact acgacgtcga ccacatcgtc ccgagagct 2580

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gaggagacgg aggaggaagc ccgaagaaga agagaaaggt ctagctagca ccagcctcaa 4200

gaacacccga atggagtctc taagctacat aataccaact tacactttac aaaatgttgt 4260

cccccaaat gtagccattc gtatctgctc ctaataaaaa gaaagtttct tcacattctc 4320

tcgag 4325

<210> 260

<211> 4325

<212> ADN

<213> Secuencia artificial

<220>

<223> Sintético: transcrito de Cas9 con AGG como los primeros tres nucleótidos para el uso con CleanCap™, 5 UTR de XBG, ORF correspondiente a la SEQ

ID NO: 204, secuencia de Kozak, y 3 UTR de XBG

<400> 260

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aggtcccgag caagaagttc aaggtcctgg gaaacacaga cagacacagc atcaagaaga 180

acctgatcgg agcactgctg ttcgacagcg gagaacagc agaagcaaca agactgaaga 240

gaacagcaag aagaagatac acaagaagaa agaacagaat ctgctacctg caggaaatct 300

tcagcaacga aatggcaaag gtcgacgaca gcttcttcca cagactggaa gaaagcttcc 360

tggtcgaaga agacaagaag cacgaaagac acccgatctt cgaaacatc gtcgacgaag 420

tcgcatacca cgaaaagtac ccgacaatct accacctgag aaagaagctg gtcgacagca 480

cagacaaggc agacctgaga ctgatctacc tggcactggc acacatgatc aagttcagag 540

gacacttcct gatcgaagga gacctgaacc cggacaacag cgacgtcgac aagctgttca 600

tccagctggc 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 ggcacagatc ggagaccagt 900

acgcagacct gttcctggca gcaaagaacc tgagcgacgc aatcctgctg agcgacatcc 960

tgagagtcaa cacagaaatc acaaaggcac cgctgagcgc aagcatgac aagagatacg 1020

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agtacaagga aatcttcttc gaccagagca agaacggata cgcaggatac atcgacggag 1140

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tcctggacaa cgaagaaaac gaagacatcc tggaagacat cgtcctgaca ctgacactgt 1920

tcgaagacag agaaatgatc gaagaaagac tgaagacata cgcacacctg ttcgacgaca 1980

aggatcatgaa gcagctgaag agaagaagat acacaggatg gggaagactg agcagaaaagc 2040

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aaggaaatcaa ggaactggga agccagatcc tgaaggaaca cccggtcgaa aacacacagc 2460

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aggaaactgga catcaacaga ctgagcgact acgacgtcga ccacatcgtc ccgcagagct 2580

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acgcatacct gaacgcagtc gtcggaacag cactgatcaa gaagtaccg aagctggaaa 3060

gcgaattcgt ctacggagac tacaaggtct acgacgtcag aaagatgac gcaaagagcg 3120

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acggagaaac aggagaaatc gtctgggaca agggaagaga cttcgcaaca gtcagaaaagg 3300

tcctgagcat gccgcaggtc aacatcgtca agaagacaga agtccagaca ggaggattca 3360

gcaaggaaaag catcctgccg aagagaaaaca gcgacaagct gatcgcaaga aagaaggact 3420

gggacccgaa gaagtacgga ggattcgaca gcccgacagt cgcatacagc gtcctggtcg 3480

tcgcaaaggt cgaaaaggga aagagcaaga agctgaagag cgtcaaggaa ctgctgggaa 3540

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gatacaagga agtcaagaag gacctgatca tcaagctgcc gaagtacagc ctgttcgaac 3660

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tggcactgcc gagcaagtac gtcaacttc tgtacctggc aagccactac gaaaagctga 3780

agggaagccc ggaagacaac gaacagaagc agctgttcgt cgaacagcac aagcactacc 3840

tggacgaaat catcgaacag atcagcgaat tcagcaagag agtcacacctg gcagacgcaa 3900

acctggacaa ggtcctgagc gcatacaaca agcacagaga caagccgatc agagaacagg 3960

cagaaaacat catccacctg ttcaactga caaacctggg agcaccggca gcattcaagt 4020

acttcgacac aacaatcgac agaaagagat acacaagcac aaaggaagtc ctggacgcaa 4080

cactgatcca ccagagcatc acaggactgt acgaaacaag aatcgacctg agccagctgg 4140

gaggagacgg aggaggaagc ccgaagaaga agagaaaggt ctagctagca ccagcctcaa 4200

gaacacccga atggagtctc taagtacat aataccaact tacactttac aaaatgttgt 4260

cccccaaat gtagccattc gtatctgctc ctaataaaaa gaaagtttct tcacattctc 4320

tcgag 4325

<210> 261

<211> 4411

<212> ADN

<213> Secuencia artificial

<220>

<223> Sintético: transcrito de Cas9 con AGG como los primeros tres nucleótidos para el uso con CleanCap™, 5 UTR de HSD, ORF correspondiente a la SEQ ID NO: 204, secuencia de Kozak, y 3 UTR de ALB

<400> 261

aggccccga gtcggcgctc agcggctctg cttgttcgtg tgtgtgtcgt tgcaggcctt 60

attcggtacc gccaccatgg acaagaagta cagcatcgga ctggacatcg gaacaaacag 120

cgtcggatgg gcagtcacca cagacgaata caaggtcccg agcaagaagt tcaaggtcct 180

gggaaacaca gacagacaca gcatcaagaa gaacctgac ggagcactgc tggtcgacag 240

cggagaaaca gcagaagcaa caagactgaa gagaacagca agaagaagat acacaagaag 300

aaagaacaga atctgctacc tgcaggaaat cttcagcaac gaaatggcaa aggtcgacga 360

cagcttcttc cacagactgg aagaaagctt cctggtcgaa gaagacaaga agcacgaaag 420

acacccgatc ttcggaaaca tcgtcgacga agtcgcatac cacgaaaagt acccgacaat 480

ctaccacctg agaaagaagc tggtcgacag cacagacaag gcagacctga gactgatcta 540

cctggcactg gcacacatga tcaagttcag aggacacttc ctgatcgaag gagacctgaa 600

cccggacaac agcgacgtcg acaagctgtt catccagctg gtccagacat acaaccagct 660

gttcgaagaa aacccgatca acgcaagcgg agtcgacgca aaggcaatcc tgagcgcaag 720

actgagcaag agcagaagac tggaaaacct gatcgcacag ctgccgggag aaaagaagaa 780

cggactgttc ggaaacctga tcgcactgag cctgggactg acaccgaact tcaagagcaa 840

cttcgacctg gcagaagacg caaagctgca gctgagcaag gacacatacg acgacgacct 900

ggacaacctg ctggcacaga tcggagacca gtacgcagac 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 agcatccgc accagatcca 1320

cctgggagaa ctgcacgcaa tcctgagaag acaggaagac ttctaccgt tcctgaagga 1380

caacagagaa aagatcgaag agatcctgac attcagaatc ccgtactacg tcggaccgct 1440

ggcaagagga aacagcagat tcgcatggat gacaagaaag agcgaagaaa caatcacacc 1500

gtggaacttc gaagaagtcg tcgacaaggg agcaagcgca cagagcttca tcgaaagaat 1560

gacaaacttc gacaagaacc tgccgaacga aaaggtcctg ccgaagcaca gcctgctgta 1620

cgaatacttc acagtctaca acgaactgac aaaggtcaag tacgtcacag aaggaatgag 1680

aaagccggca ttcctgagcg gagaacagaa gaaggcaatc gtcgacctgc tgttcaagac 1740

aaacagaaag gtcacagtca agcagctgaa ggaagactac ttcaagaaga tcgaatgctt 1800

cgacagcgtc gaaatcagcg gagtcaaga cagattcaac gcaagcctgg gaacatacca 1860

cgacctgctg aagatcatca aggacaagga cttctggac aacgaagaaa acgaagacat 1920

cctggaagac atcgtcctga cactgacact gttcgaagac agagaaatga tcgaagaaag 1980

actgaagaca tacgcacacc tgttcgacga caaggtcatg aagcagctga agagaagaag 2040

atacacagga tggggaagac tgagcagaaa gctgatcaac ggaatcagag acaagcagag 2100

cgaaagaca atcctggact tcctgaagag cgacggattc gcaaacagaa acttcatgca 2160

gctgatccac gacgacagcc tgacattcaa ggaagacatc cagaaggcac aggtcagcgg 2220

acaggagac agcctgcacg aacacatcgc aaacctggca ggaagcccgg caatcaagaa 2280

gggaatcctg cagacagtca aggtcgtcga cgaactggc aaggtcatgg gaagacacaa 2340

gccggaaaac atcgtcatcg aaatggcaag agaaaaccag acaacacaga agggacagaa 2400

gaacagcaga gaaagaatga agagaatcga agaaggaatc aaggaactgg gaagccagat 2460

cctgaaggaa caccggctcg aaaacacaca gctgcagaac gaaaagctgt acctgtacta 2520

cctgcagaac ggaagagaca tgtacgtcga ccaggaactg gacatcaaca gactgagcga 2580

ctacgacgtc gaccacatcg tcccgagag 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 agacagtgg 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 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

cagccccgaca gtcgcataca gcgtcctggt cgtcgcaaag gtcgaaaagg gaaagagcaa 3540

gaagctgaag agcgtcaagg aactgctggg aatcacaatc atggaaagaa gcagcttcga 3600

aaagaacccg atcgacttcc tggaagcaaa gggatacaag gaagtcaaga aggacctgat 3660

catcaagctg ccgaagtaca gcctgttcga actggaaaac ggaagaaaga gaatgctggc 3720

aagcgagga gaactgcaga agggaaacga actggcactg ccgagcaagt acgtcaactt 3780

cctgtacctg gcaagccact acgaaaagct gaagggaagc ccggaagaca acgaacagaa 3840

gcagctgttc gtcgaacagc acaagcacta cctggacgaa atcatcgaac agatcagcga 3900

attcagcaag agagtcattc tggcagacgc aaacctggac aaggtcctga gcgcatacaa 3960

caagcacaga gacaagccga tcagagaaca ggcagaaaac atcatccacc tggtcacact 4020

gacaaacctg ggagcaccgg cagcattcaa gtacttcgac acaacaatcg acagaaagag 4080

atacacaagc acaaaggaag tcctggacgc aacctgatc caccagagca tcacaggact 4140

gtacgaaaca agaatcgacc tgagccagct gggaggagac ggaggaggaa gcccgaaaga 4200

gaagagaaag gtctagctag ccatcacatt taaaagcatc tcagcctacc atgagaataa 4260

gagaaagaaa atgaagatca atagcttatt catctctttt tcttttcgt tgggtgaaag 4320

ccaacaccct gtctaaaaaa cataaatttc tttaatcatt ttgcctcttt tctctgtgct 4380

tcaattaata aaaaatggaa agaacctga g 4411

<210> 262

<400> 262

000

<210> 263

<211> 93

<212> ADN

<213> Secuencia artificial

<220>

<223> Sintético: secuencia poli-A 100

<400> 263

aaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 60

aaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaa 93

<210> 264

<211> 44

<212> ADN

<213> Secuencia artificial

<220>

<223> Sintético: ARN de guía única G209 dirigido al gen TTR de ratón

<400> 264

aaataagaga gaaaagaaga gtaagaagaa atataagagc cacc 44

<210> 265

<211> 3312

<212> ADN

<213> Secuencia artificial

<220>

<223> Sintético: ORF que codifica Cas9 de Neisseria meningitidis que usa codones de mínima

uridina, con codones de inicio y parada

<400> 265

atggcagcat tcaagccgaa 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 gtctgcagg cagcaaactt cgacgaaaac	300
ggactgatca agtcgctgcc gaacacaccg tggcagctga gagcagcagc actggacaga	360
aagctgacac cgctggaatg gtcggcagtc ctgctgcacc tgatcaagca cagaggatac	420
ctgtcgaga gaaagaacga aggagaaaca gcagacaagg aactgggagc actgctgaag	480
ggagtgcgag gaaacgcaca cgactgcag acaggagact tcagaacacc ggcagaactg	540
gcactgaaca agttcgaaaa ggaatcggga cacatcagaa accagagatc ggactactcg	600
cacacattct cgagaaagga cctgcaggca gaactgatcc tgctgttcga aaagcagaag	660
gaattcggaa acccgcacgt ctggggagga ctgaaggaag gaatcgaaac actgctgatg	720
acacagagac cggcactgtc gggagacgca gtccagaaga tgctgggaca ctgcacattc	780

gaaccggcag aaccgaaggc agcaaagaac acatacacag cagaaagatt catctggctg 840

acaaagctga acaacctgag aatcctggaa cagggatcgg aaagaccgct gacagacaca 900

gaaagagcaa cactgatgga cgaaccgtac agaaagtcga agctgacata cgcacaggca 960

agaaagctgc tgggactgga agacacagca ttcttcaagg gactgagata cggaaaggac 1020

aacgcagaag catcgacact gatggaaatg aaggcatacc acgcaatctc gagagcactg 1080

gaaaaggaag gactgaagga caagaagtcg ccgctgaacc tgtcgccgga actgcaggac 1140

gaaatcgga cagcattctc gctgttcaag acagacgaag acatcacagg aagactgaag 1200

gacagaatcc agccggaaat cctggaagca ctgctgaagc acatctcgtt cgacaagttc 1260

gtccagatct cgctgaaggc actgagaaga atcgccccgc tgatggaaca gggaaagaga 1320

tacgacgaag catgcgaga aatctacgga gaccactacg gaaagaagaa cacagaagaa 1380

aagatctacc tgccgccgat cccggcagac gaaatcagaa acccggtcgt cctgagagca 1440

ctgtcgagg caagaaaggt catcaacgga gtcgtcagaa gatacggatc gccggcaaga 1500

atccacatcg aaacagcaag agaagtcgga aagtcgttca aggacagaaa ggaaatcgaa 1560

aagagacagg aagaaaacag aaaggacaga gaaaaggcag cagcaaagtt cagagaatac 1620

ttcccgaact tcgtcgga accgaagtcg aaggacatcc tgaagctgag actgtacgaa 1680

cagcagcacg gaaagtcct gtactcggga aaggaaatca acctgggaag actgaacgaa 1740

aagggatacg tcgaaatcga ccacgcactg ccgttctcga gaacatggga cgactcgttc 1800

aacaacaagg tcctggtcct gggatcggaa aaccagaaca agggaaacca gacaccgtac 1860

gaatacttca acggaaagga caactcgaga gaatggcagg aattcaaggc aagagtcgaa 1920

acatcgagat tcccgagatc gaagaagcag agaatcctgc tgcagaagtt cgacgaagac 1980

ggattcaagg aaagaaacct gaacgacaca agatacttca acagattcct gtgccagttc 2040

gtcgcagaca gaatgagact gacaggaaag ggaaagaaga gagtcttcgc atcgaacgga 2100

cagatcacia acctgctgag aggattctgg ggactgagaa aggtcagagc agaaaacgac 2160

agacaccacg cactggacgc agtcgtcgtc gcatgctcga cagtcgcaat gcagcagaag 2220

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

cagggaacaca tggaaacagt caagtcggca aagagactgg acgaaggagt ctcgtcctg 2580
 agagtcccg tgacacagct gaagctgaag gacctggaaa agatgggtcaa cagagaaaga 2640
 gaaccgaagc tgtacgaagc actgaaggca agactggaag cacacaagga cgacccggca 2700
 aaggcattcg cagaaccgtt ctacaagtac gacaaggcag gaaacagaac acagcaggtc 2760
 aaggcagtca gagtgaaca ggtccagaag acaggagtct gggtcagaaa ccacaacgga 2820
 atcgagaca acgaacaat ggtcagagta gacgtcttcg aaaagggaga caagtactac 2880
 ctggtccga tctactctg gcaggtcgca aagggaatcc tgccggacag agcagtcgtc 2940
 cagggaagg acgaagaaga ctggcagctg atcgacgact cgttcaactt caagttctcg 3000
 ctgcaccga acgacctggt cgaagtcac acaaagaagg caagaatgtt cggatacttc 3060
 gcatcgtgcc acagaggaac aggaacatc aacatcagaa tccacgacct ggaccacaag 3120
 atcggaaga acggaatcct ggaaggaatc ggagtcaaga cagcactgtc gttccagaag 3180
 taccagatcg acgaactggg aaaggaaatc agaccgtgca gactgaagaa gagaccgccg 3240
 gtcagatccg gaaagagaac agcagacgga tcggaattcg aatcgccgaa gaagaagaga 3300
 aagtcgaat ga 3312

<210> 266

<211> 3306

<212> ADN

<213> Secuencia artificial

<220>

<223> Sintético: ORF que codifica Cas9 de Neisseria meningitidis que usa codones de mínima uridina (sin codones de inicio y parada; adecuado para su inclusión en la secuencia de codificación de proteínas de fusión)

<400> 266

gcagattca agccgaactc gatcaactac atctgggac tggacatcgg aatcgcatcg 60

gtcggatggg caatggtcga aatcgacgaa gaagaaaacc cgatcagact gatcgacctg 120

ggagtcagag tcttcgaaag agcagaagtc ccgaagacag gagactcgct ggcaatggca 180

agaagactgg caagatcggc cagaagactg acaagaagaa gagcacacag actgctgaga 240

acaagaagac tgctgaagag agaaggagtc ctgcaggcag caaacttcga cgaaaacgga 300

ctgatcaagt cgctgccgaa cacaccgtgg cagctgagag cagcagcact ggacagaaag 360

ctgacaccgc tggaatggtc ggagtcctg ctgcacctga tcaagcacag aggatacctg 420

tgcgagagaa agaacgaagg agaaacagca gacaaggaac tgggagcact gctgaaggga 480

gtcgaggaa acgcacacgc actgcagaca ggagacttca gaacaccggc agaactggca 540

ctgaacaagt tcgaaaagga atcgggacac atcagaaacc agagatcgga ctactcgac 600

acattctcga gaaaggacct gcaggcagaa ctgacacctg tggtcgaaaa gcagaaggaa 660

ttcgaaacc cgcacgtctc gggaggactg aaggaaggaa tcgaaacact gctgatgaca 720

cagagaccgg cactgtcggg agacgcagtc cagaagatgc tgggacactg cacattcgaa 780

ccggcagaac cgaaggcagc aaagaacaca tacacagcag aaagattcat ctggctgaca 840

aagctgaaca acctgagaat cctggaacag ggatcggaaa gaccgctgac agacacagaa 900

agagcaacac tgatggacga accgtacaga aagtcgaagc tgacatacgc acaggcaaga 960

aagctgctgg gactggaaga cacagcattc ttcaaggac tgagatacgg aaaggacaac 1020

gcagaagcat cgacactgat ggaaatgaag gcataccacg caatctcgag agcactggaa 1080

aaggaaggac tgaaggacaa gaagtcgccg ctgaacctgt cgccggaact gcaggacgaa 1140

atcgaacag cattctcgct gttcaagaca gacgaagaca tcacaggaag actgaaggac 1200

agaatccagc cggaaatcct ggaagcactg ctgaagcaca tctcgttcga caagttcgtc 1260

cagatctcgc tgaaggcact gagaagaatc gtcccgtga tggaacaggg 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 agtcggaaaag 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 cgactgccg ttctcgagaa catgggacga ctcgttcaac 1800

aacaagggtcc tggctctggg 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

atcacaaacc tgctgagagg attctgggga ctgagaaagg tcagagcaga aaacgacaga 2160

caccacgcac tggacgcagt cgtcgtcgca tgctcgacag tcgcaatgca gcagaagatc 2220

acaagattcg tcagatacaa ggaaatgaac gcattcgacg gaaagacaat cgacaaggaa 2280

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gaagtcatga tcagagtctt cggaagccg 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 tggtaacag agaaagagaa 2640

ccgaagctgt acgaagcact gaaggcaaga ctggaagcac acaaggacga cccggcaaag 2700

gcattcgag aaccgttcta caagtacgac aaggcaggaa acagaacaca gcaggtcaag 2760

gcagtcagag tcgaacaggt ccagaagaca ggagtctggg tcagaaacca caacggaatc 2820

gcagacaacg caacaatggt cagagtagac gtcttcgaaa aggagacaa gtactacctg 2880

gtcccgatct actcgtggca ggtcgcaaag ggaatcctgc cggacagagc agtcgtccag 2940

ggaaaggacg aagaagactg gcagctgac gacgactcgt tcaactcaa gttctcgctg 3000

cacccgaacg acctggtcga agtcatacaca aagaaggcaa gaatgttcgg atacttcgca 3060

tcgtgccaca gaggaacagg aaacatcaac atcagaatcc acgacctgga ccacaagatc 3120

ggaaagaacg gaatcctgga aggaatcgga gtcaagacag cactgtcgtt ccagaagtac 3180

cagatcgacg aactgggaaa ggaaatcaga ccgtgcagac tgaagaagag accgccggtc 3240

agatccggaa agagaacagc agacggatcg gaattcgaat cgccgaagaa gaagagaaag 3300

gtcgaa 3306

<210> 267

<211> 3636

<212> ADN

<213> Secuencia artificial

<220>

<223> Sintético: transcrito que comprende la SEQ ID NO: 265 (que codifica Cas9 de
Neisseria meningitidis)

<400> 267

gggagaccga agctggctag cgtttaaact taagcttgga tccgccacca tggcagcatt 60

caagccgaac tcgatcaact acatcctggg actggacatc ggaatcgcac cggtcggatg 120

ggcaatggtc gaaatcgacg aagaagaaaa cccgatcaga 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 ggcagctgag agcagcagca ctggacagaa agctgacacc 420

gctggaatgg tcggcagtcc tgctgcacct gatcaagcac agaggatacc tgtcgagag 480

aaagaacgaa ggagaaacag cagacaagga actgggagca ctgctgaagg gagtgcagg 540

aaacgcacac gactgcaga caggagactt cagaacaccg gcagaactgg cactgaacaa 600

gttcgaaaag gaatcgggac acatcagaaa ccagagatcg gactactcg acacattctc 660

gagaaaggac ctgcaggcag aactgatcct gctgttcgaa aagcagaagg aattcggaaa 720

ccgcacgtc tcgggaggac tgaaggaagg aatcgaaaca ctgctgatga cacagagacc 780

ggcactgtcg ggagacgcag tccagaagat gctgggacac tgcacattcg aaccggcaga 840

accgaaggca gcaaagaaca catacacagc agaaagattc atctggctga caaagctgaa 900

caacctgaga atcttgaac agggatcgga aagaccgtg 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 gtcgccgaa ctgcaggacg aaatcggaac 1200

agcattctcg ctgttcaaga cagacgaaga catcacagga agactgaagg acagaatcca 1260

gccggaaatc ctggaagcac tgctgaagca catctcggtc gacaagttcg tccagatctc 1320

gctgaaggca ctgagaagaa tcgtcccgtc gatggaacag ggaaagagat acgacgaagc 1380

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 ccactccac tgtcctttcc taataaaatg aggaaattgc atcgattgt 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 caaguaaaaa 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

acgcaaaauau 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 aaaauaaggc 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

13