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(54) **SIRNA TARGETING PITUITARY TUMOR-TRANSFORMING 1 (PTTG1)**

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Continuation-in-part of application No. 10/714,333, filed on Nov. 14, 2003.

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C07H 21/02 (2006.01)

(52) **U.S. Cl.** **536/24.1**

(57) **ABSTRACT**

Efficient sequence specific gene silencing is possible through the use of siRNA technology. By selecting particular siRNAs by rational design, one can maximize the generation of an effective gene silencing reagent, as well as methods for silencing genes. Methods, compositions, and kits generated through rational design of siRNAs are disclosed including those directed to PTTG1.

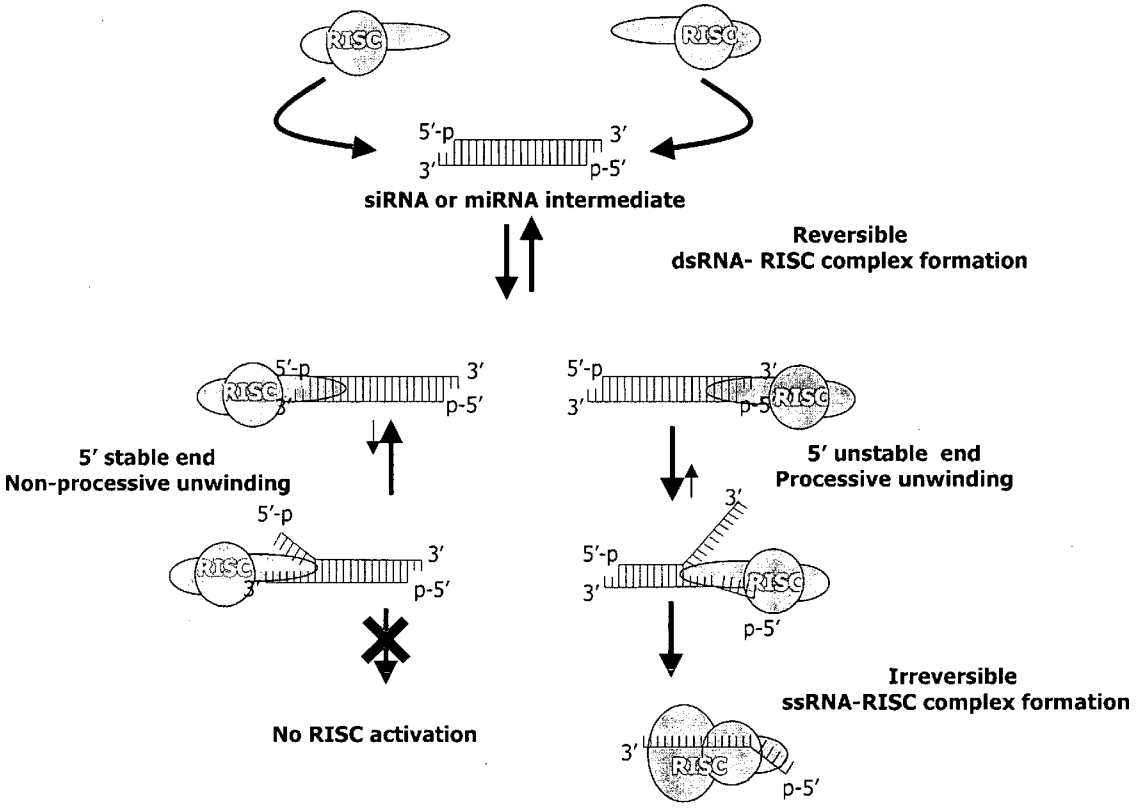


Figure 1

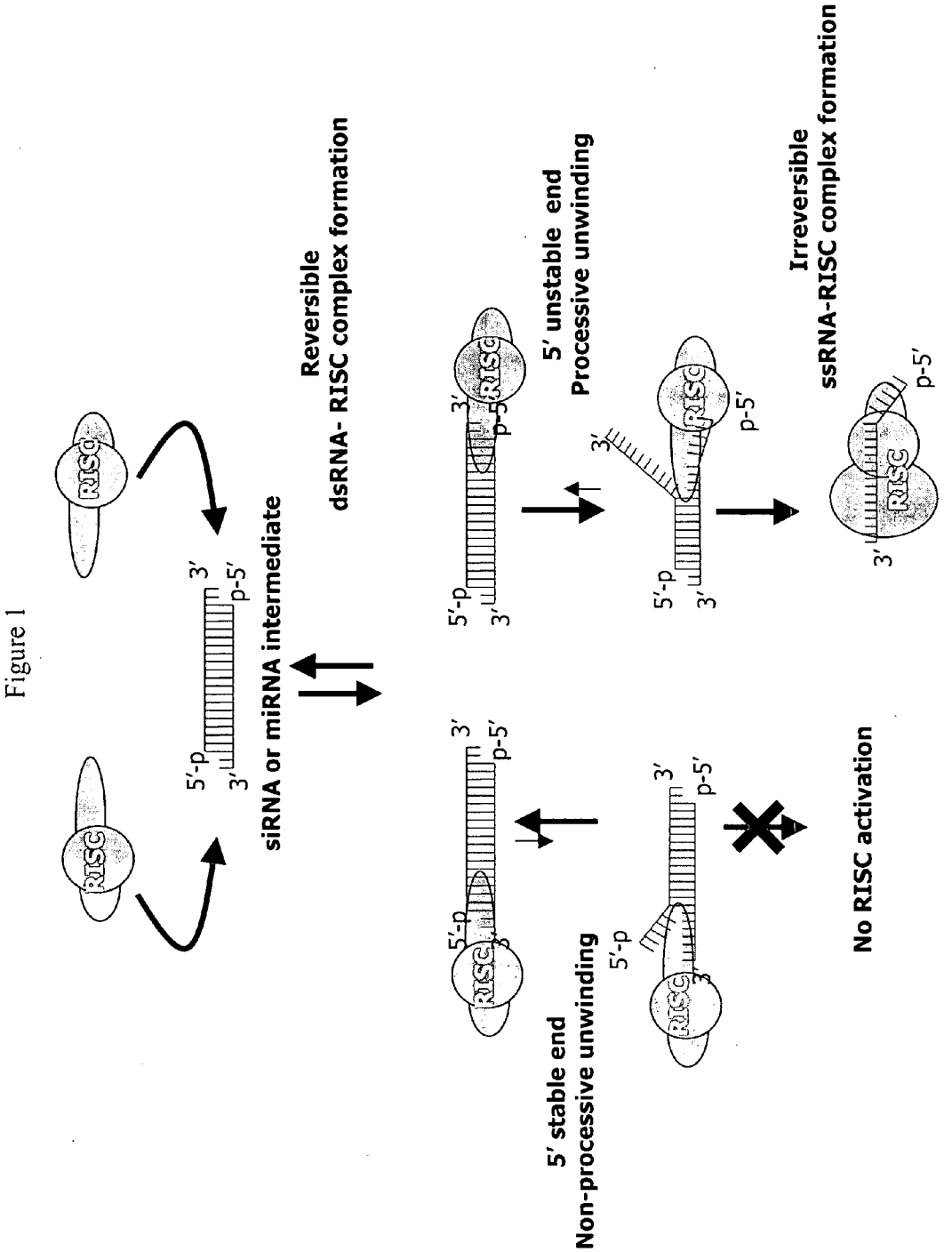

RISC
5′-p
3′
3′
p-5′
siRNA or miRNA intermediate
Reversible
dsRNA- RISC complex formation
5′ unstable end
Processive unwinding
Irreversible
ssRNA-RISC complex formation
5′ stable end
Non-processive unwinding
No RISC activation

Figure 2

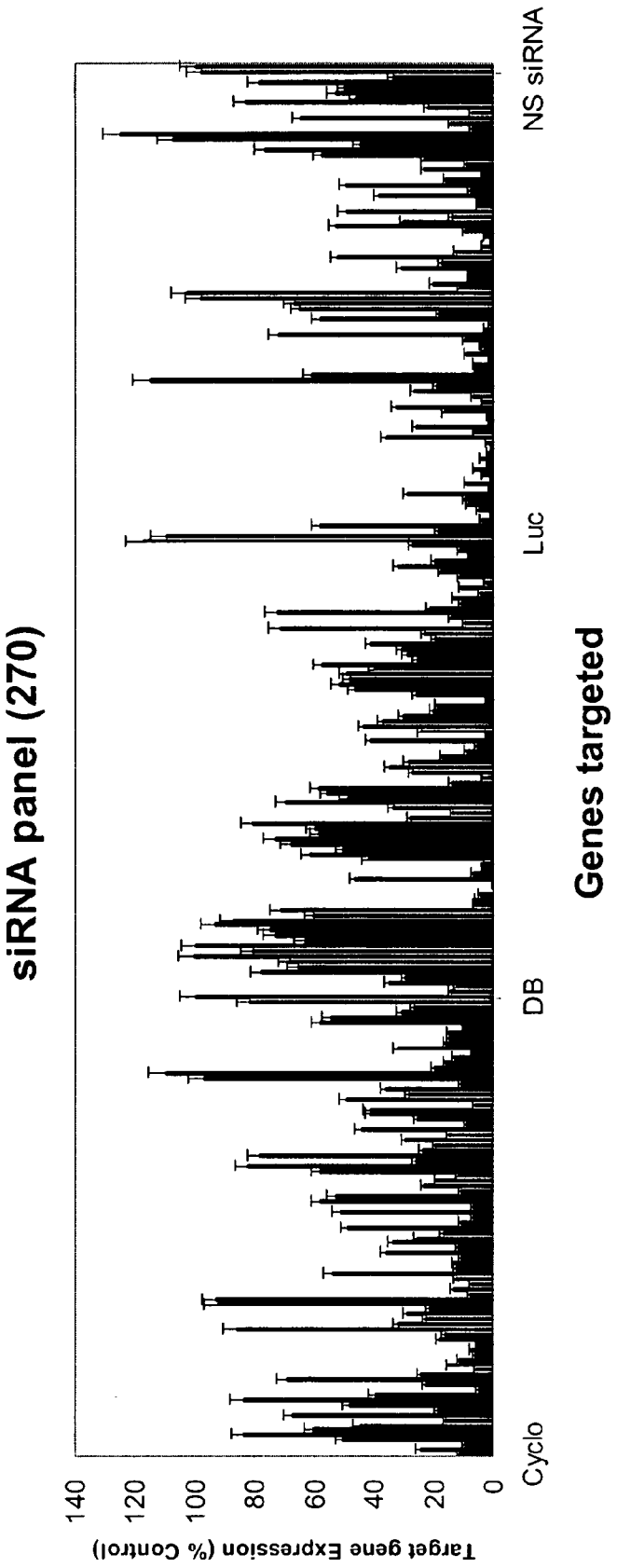
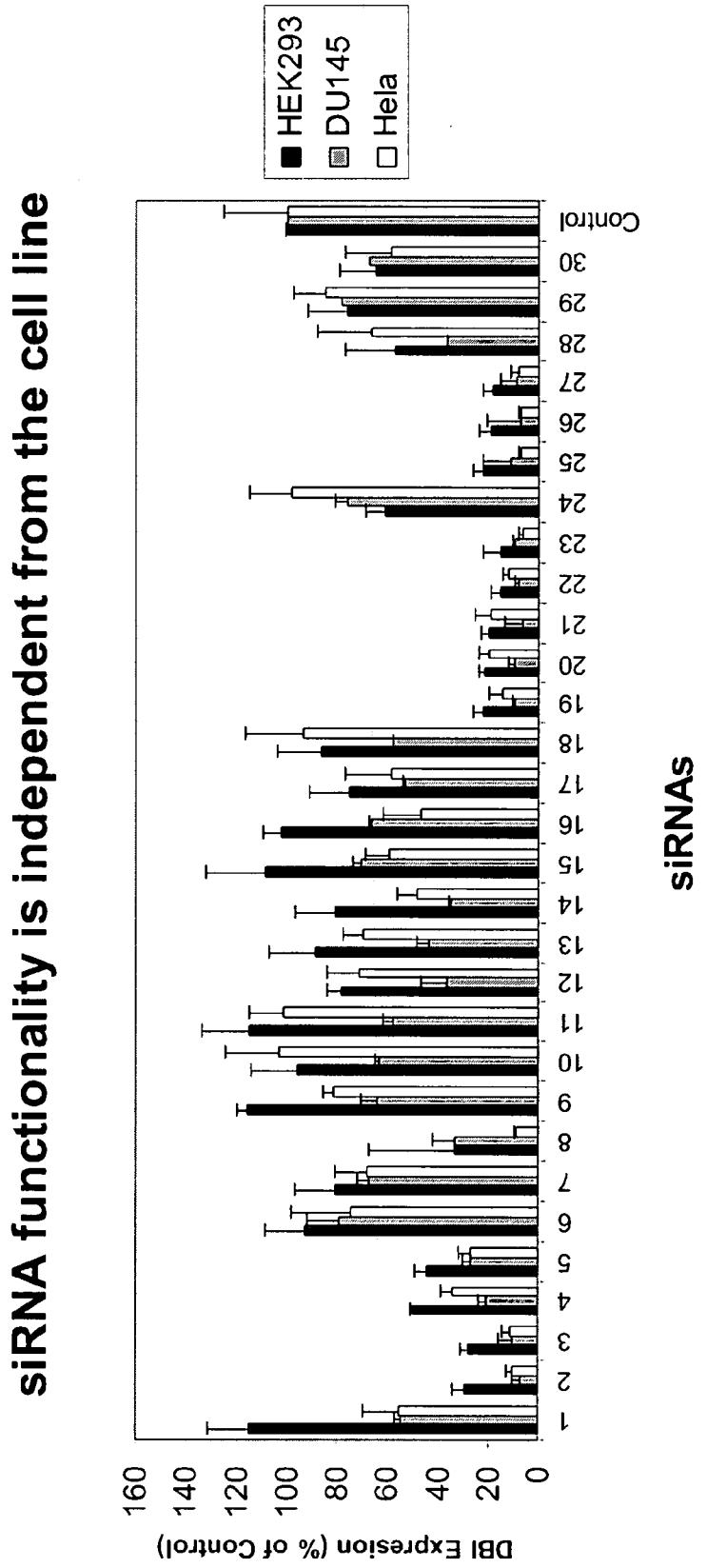

siRNA panel (270)
Target gene Expression (% Control)
140
120
100
80
60
40
20
0
Cyclo
DB
Luc
NS siRNA
Genes targeted

Figure 3a


siRNA functionality is independent from the cell line
HEK293
DU145
Hela
DBI Expression (% of Control)
0
20
40
60
80
100
120
140
160
siRNAs
Control
30
29
28
27
26
25
24
23
22
21
20
19
18
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1

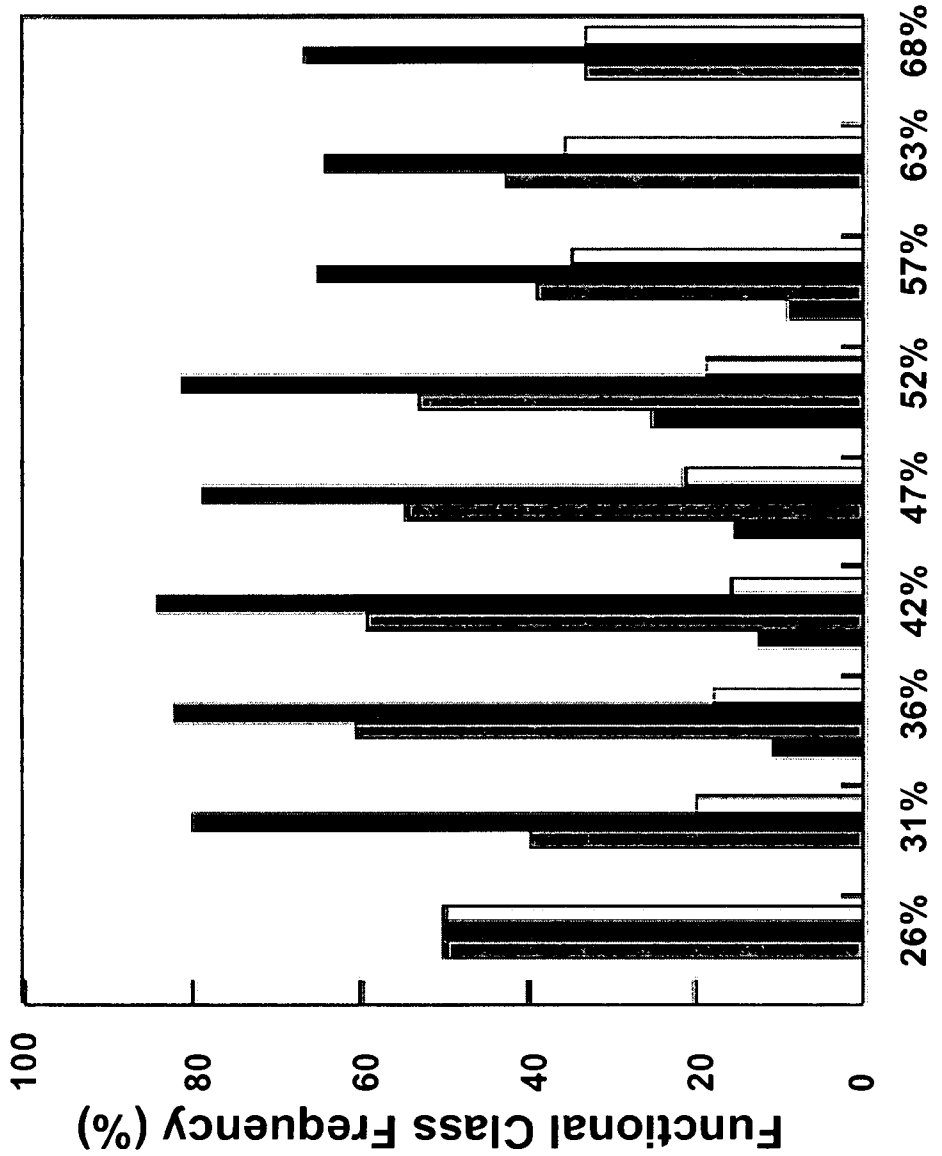

Functional Class Frequency (%)
0
20
40
60
80
100
26%
31%
36%
42%
47%
52%
57%
63%
68%

FIGURE 3B

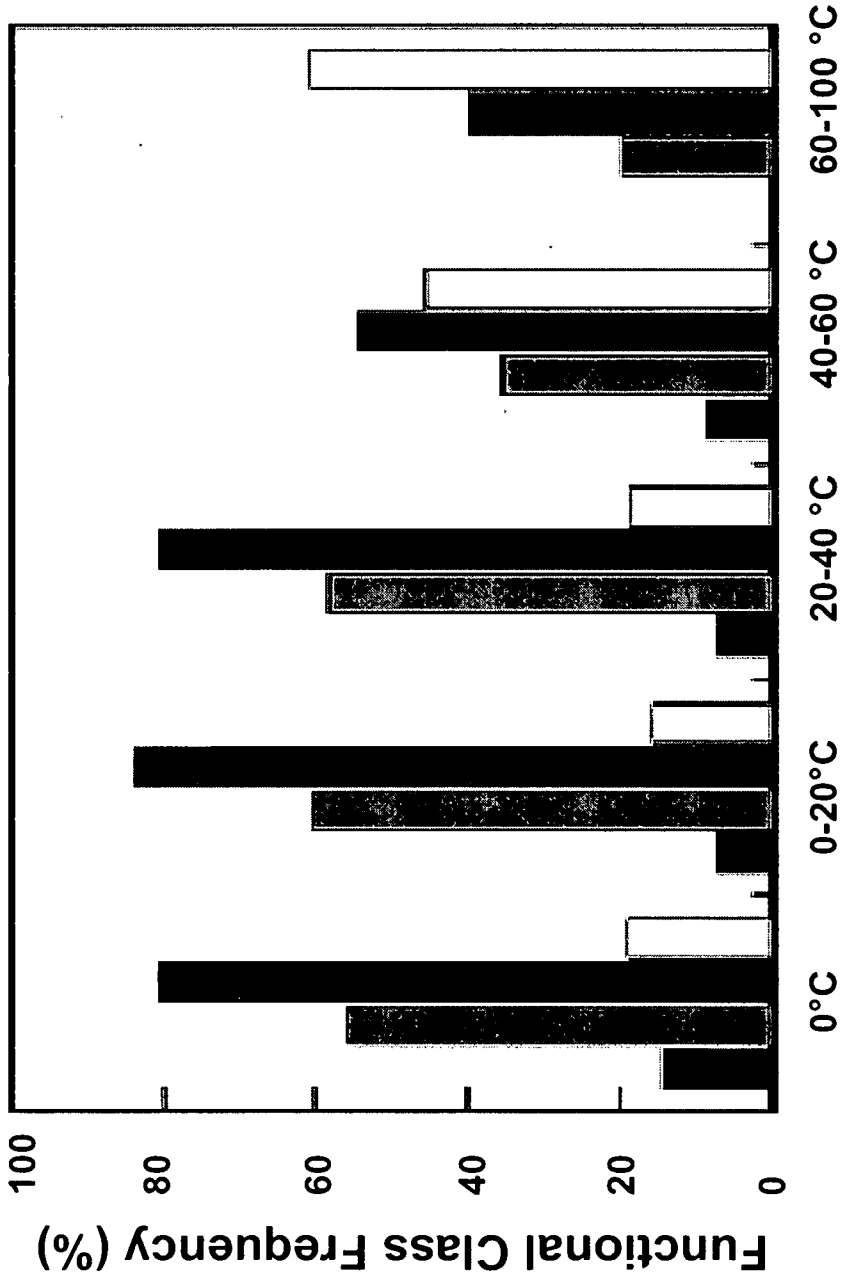

Functional Class Frequency (%)
100
80
60
40
20
0
0°C
0-20°C
20-40 °C
40-60 °C
60-100 °C
Tm

FIGURE 3C

Figure 4A

Figure 4B

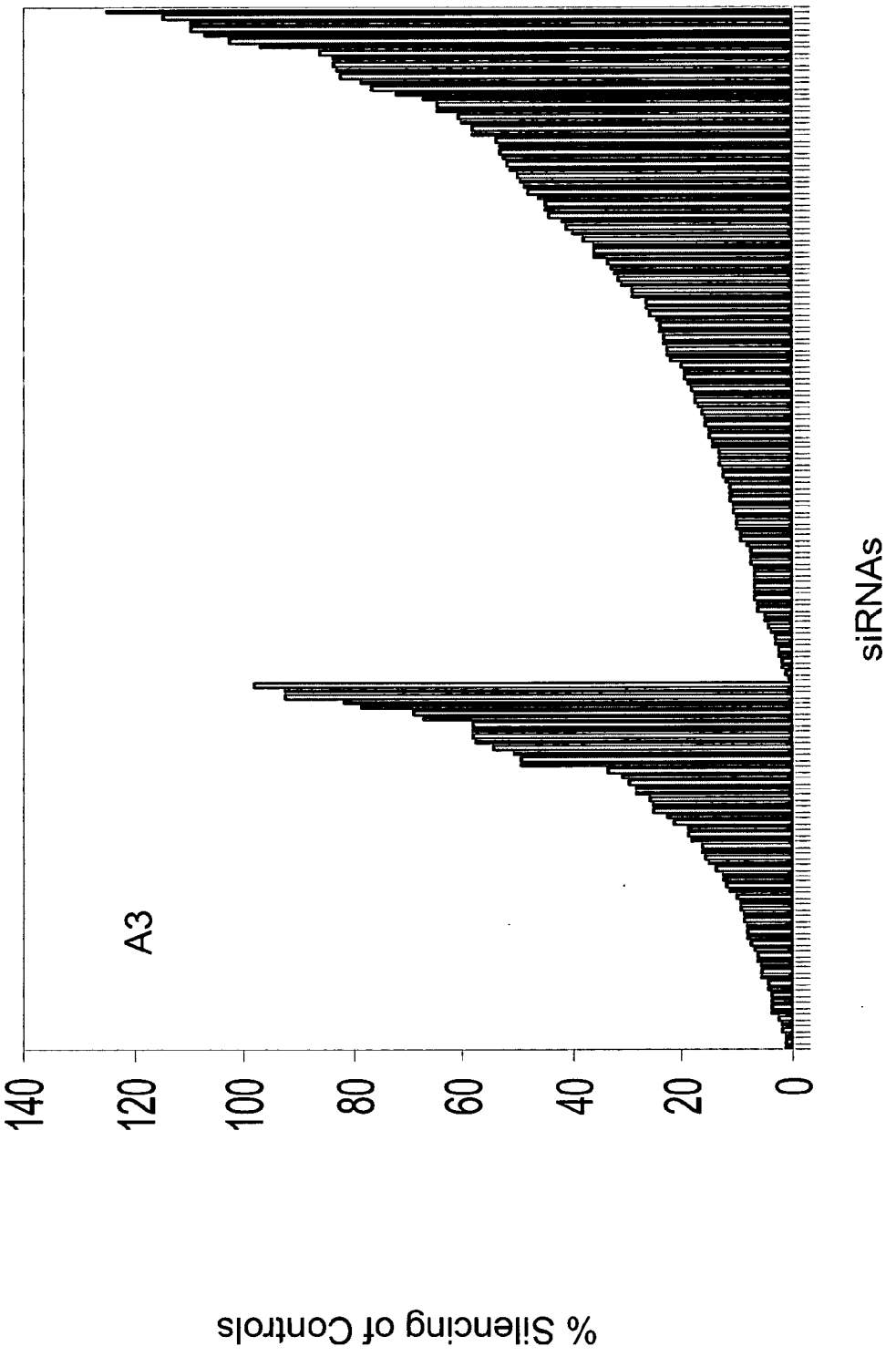


Figure 4C

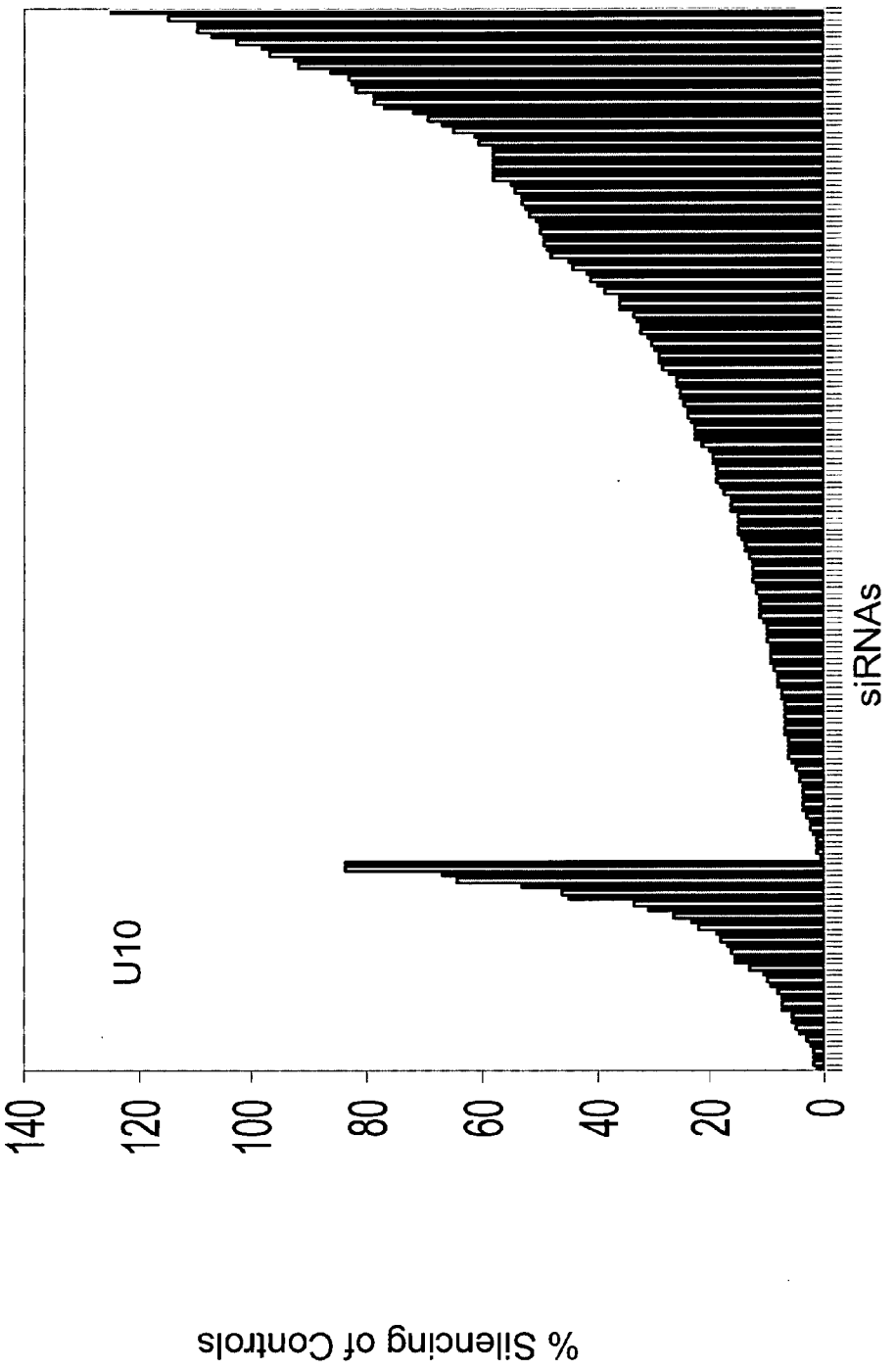


Figure 4D

Figure 4E

Figure 5A

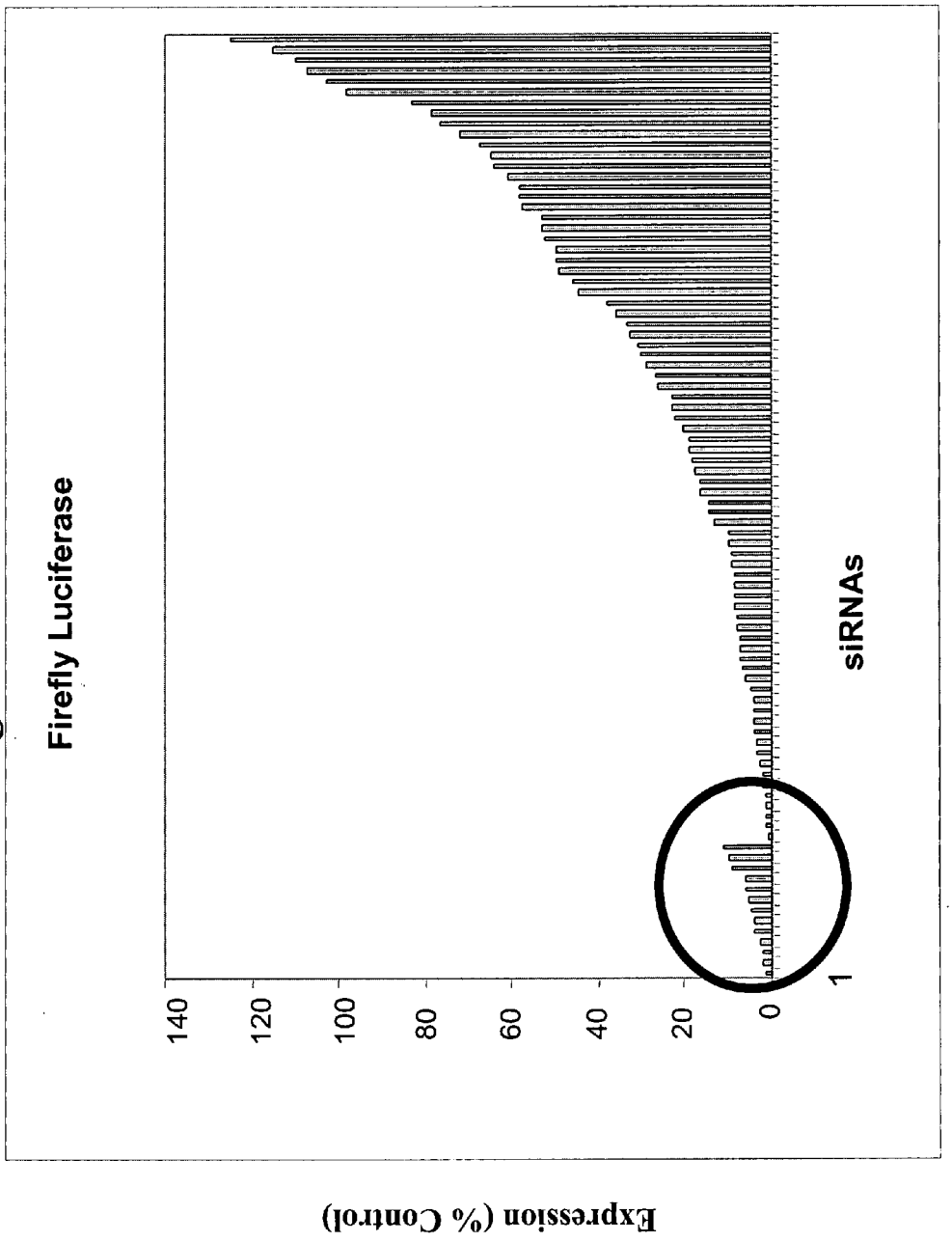

Firefly Luciferase
Expression (% Control)
140
120
100
80
60
40
20
0
1
siRNAs

Figure 5B

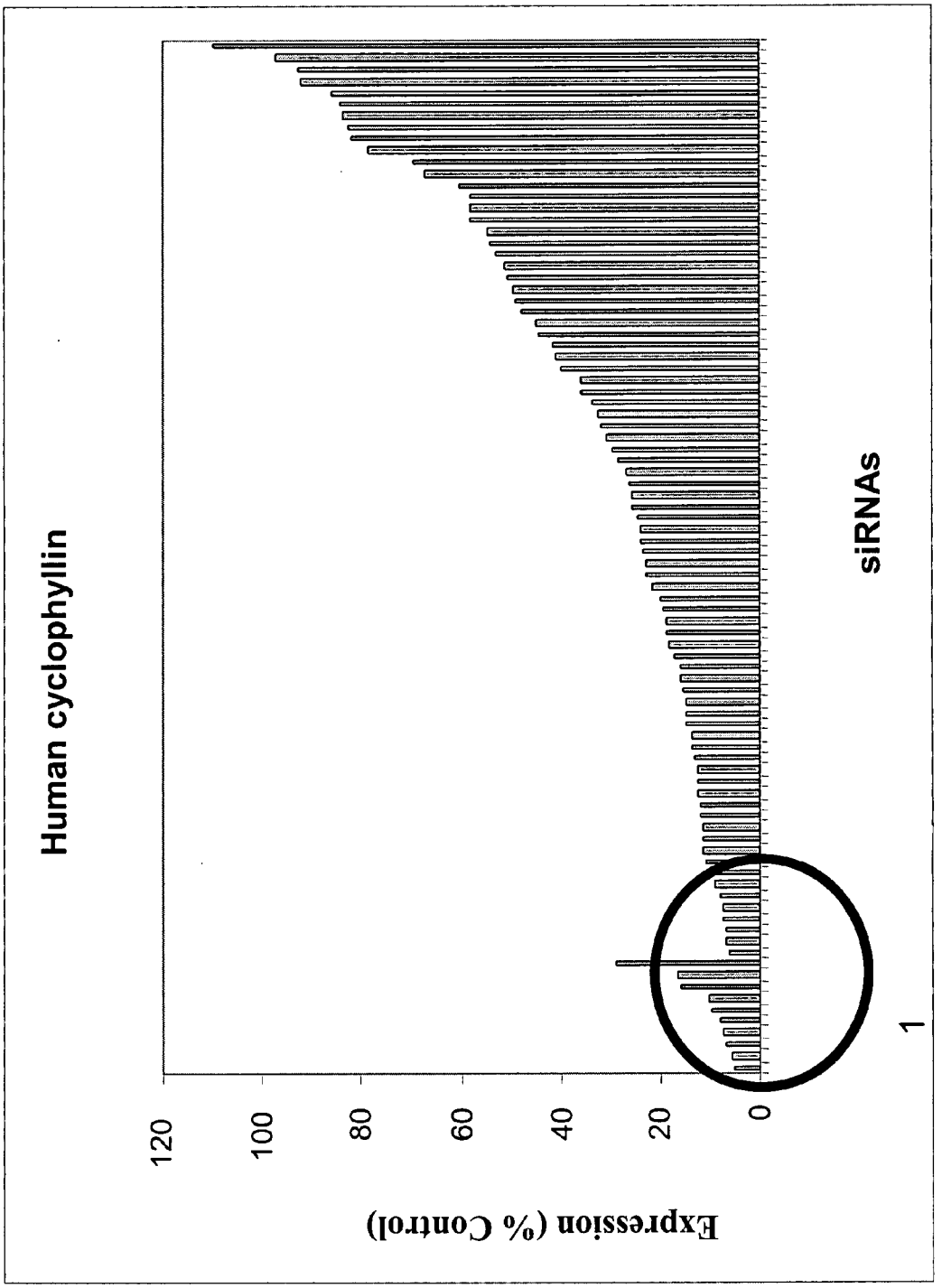

Human cyclophyllin
Expression (% Control)
120
100
80
60
40
20
0
1
siRNAs

Figure 6a

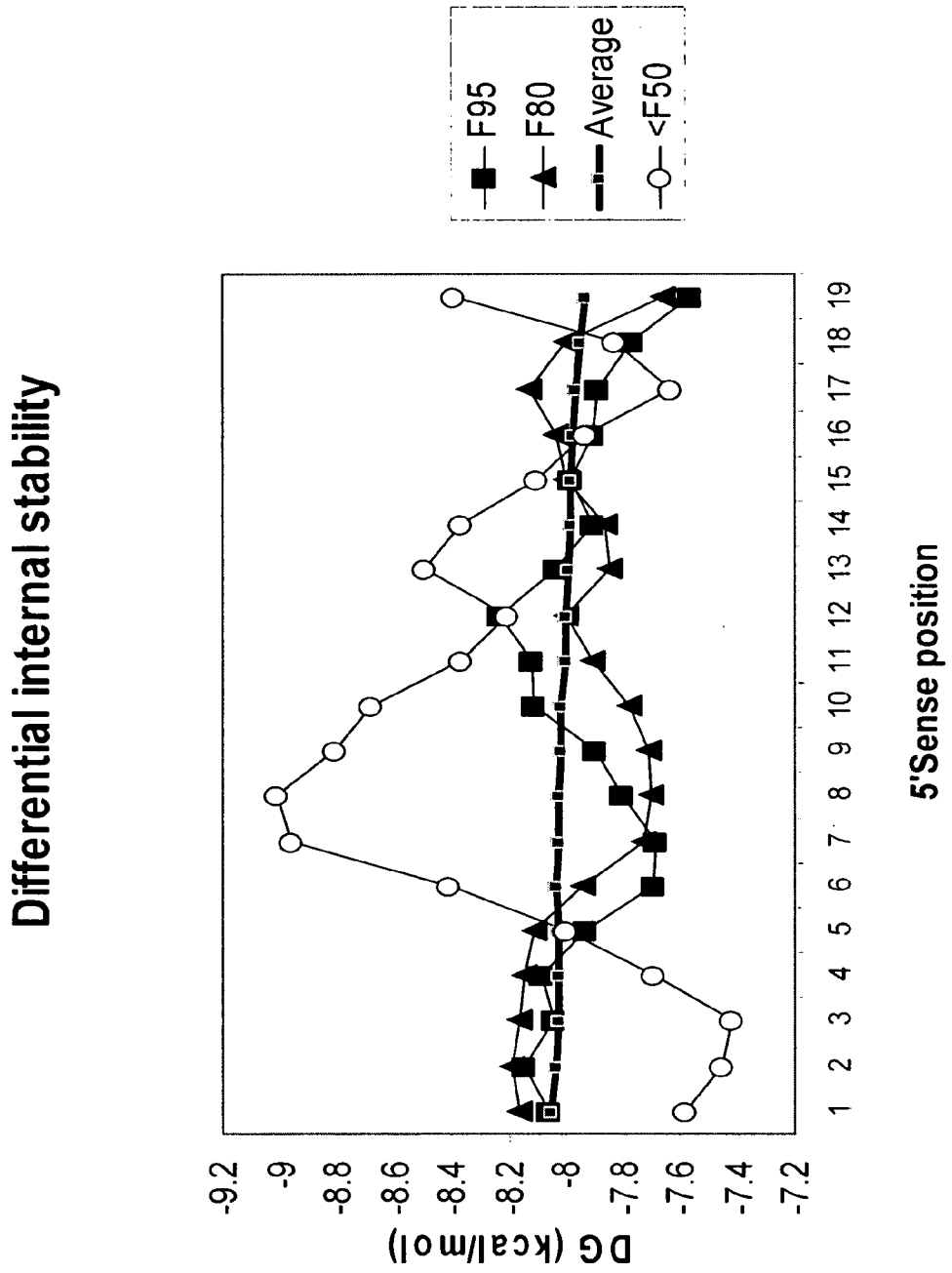
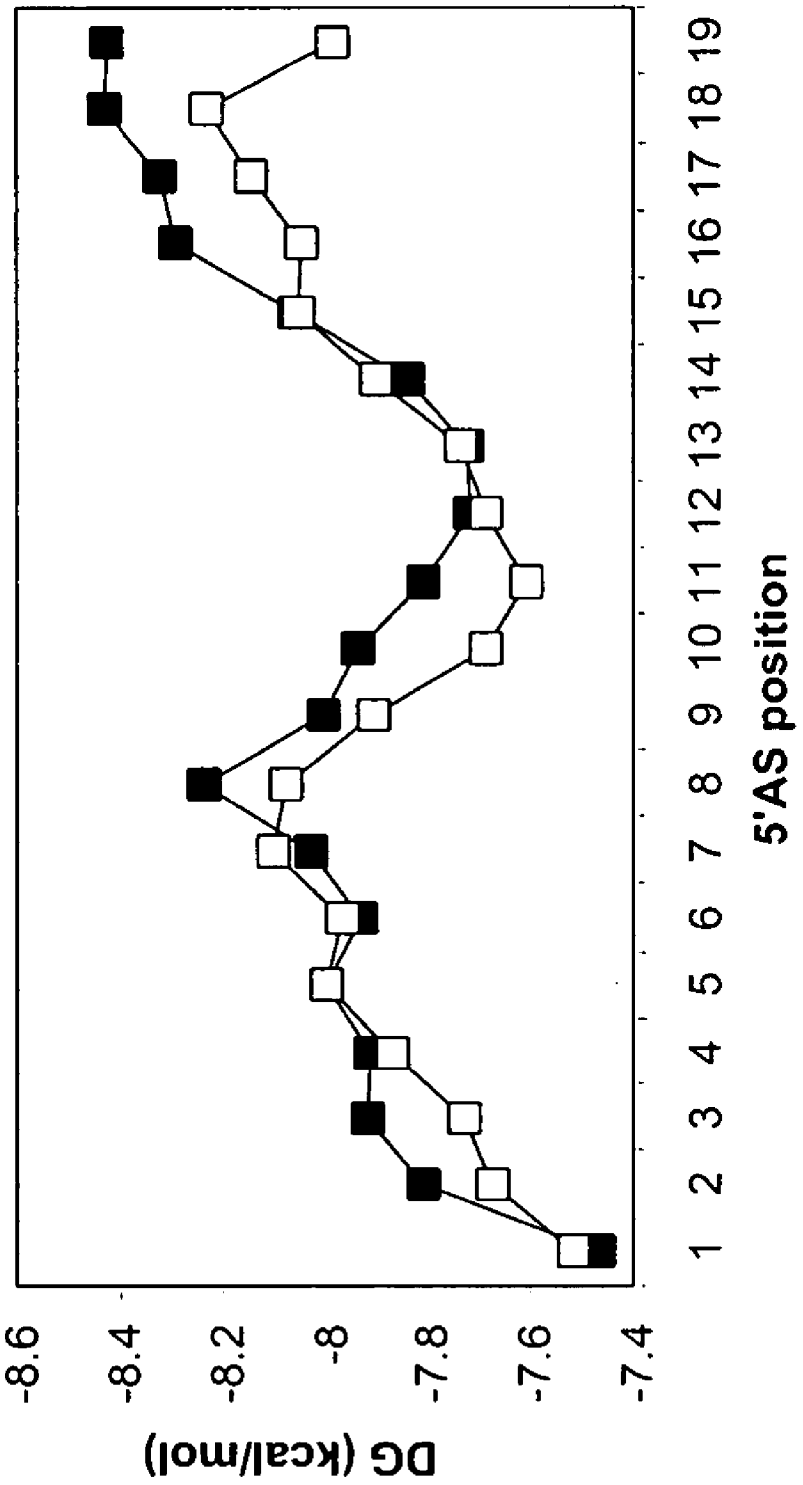

Differential internal stability
F95
F80
Average
<F50
DG (kcal/mol)
-9.2
-9
-8.8
-8.6
-8.4
-8.2
-8
-7.8
-7.6
-7.4
-7.2
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
5'Sense position

Figure 6b


DG (kcal/mol)
-8.6
-8.4
-8.2
-8
-7.8
-7.6
-7.4
5'AS position
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19

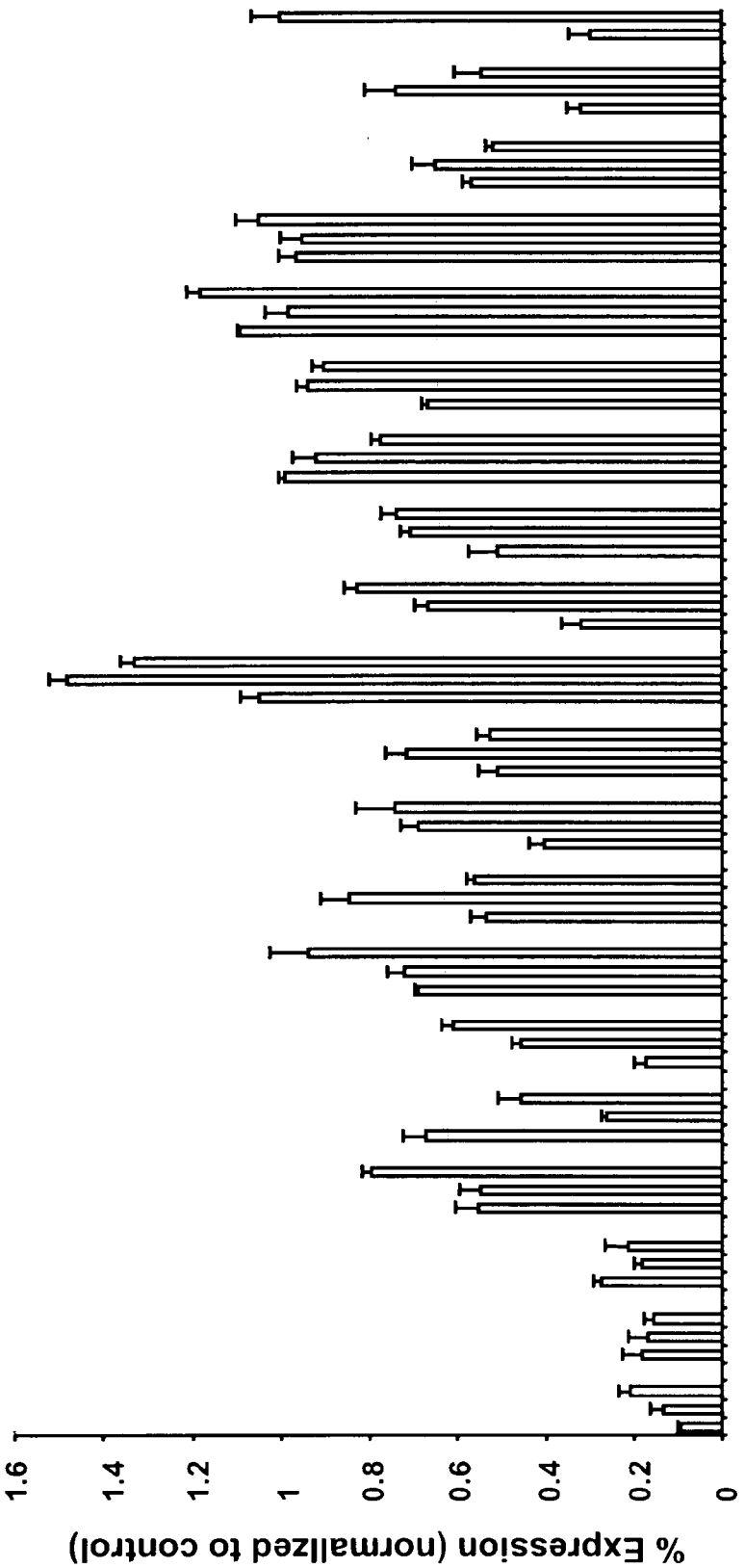

% Expression (normalized to control)
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
siRNA 100 nM

FIGURE 7

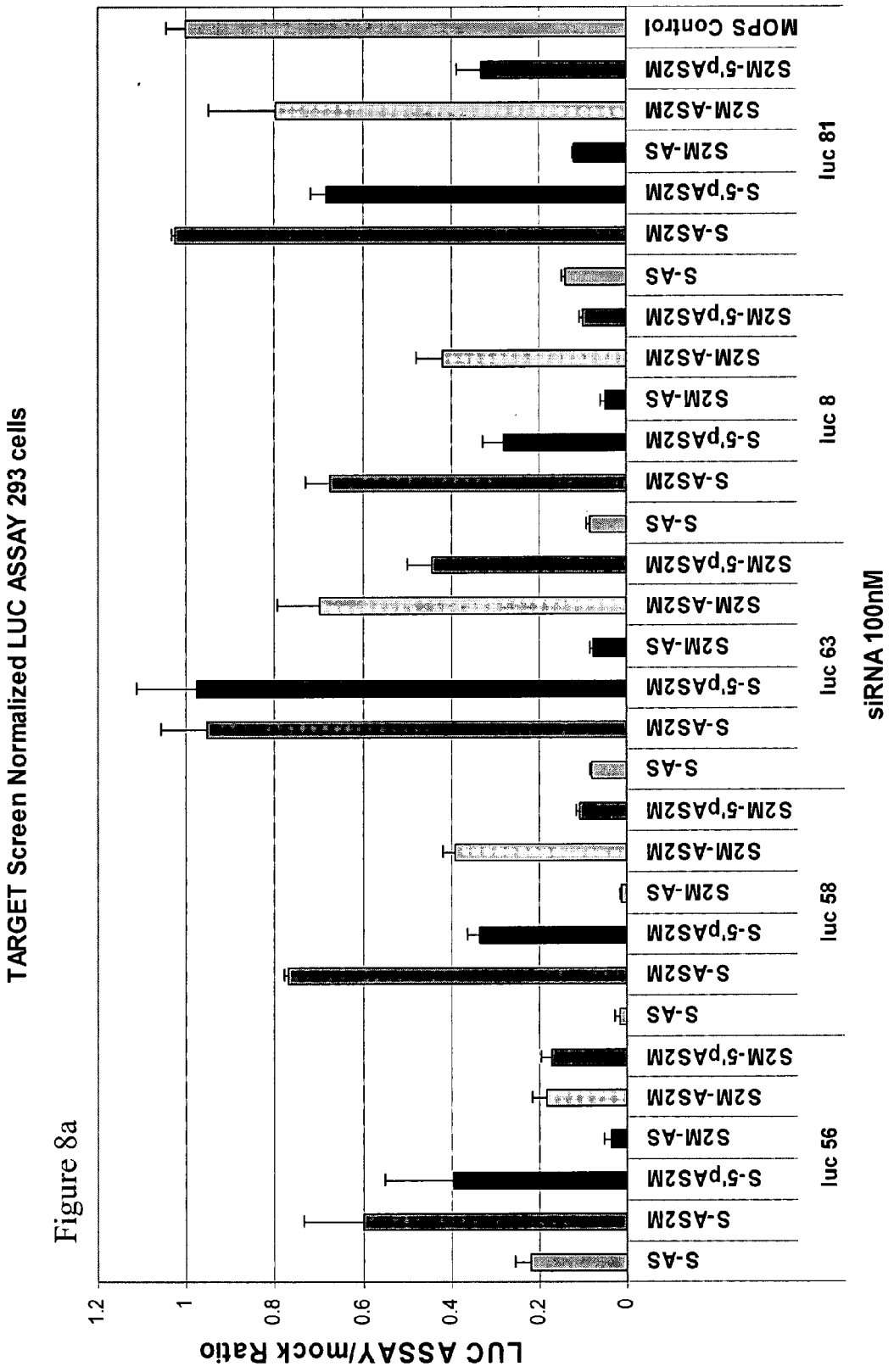
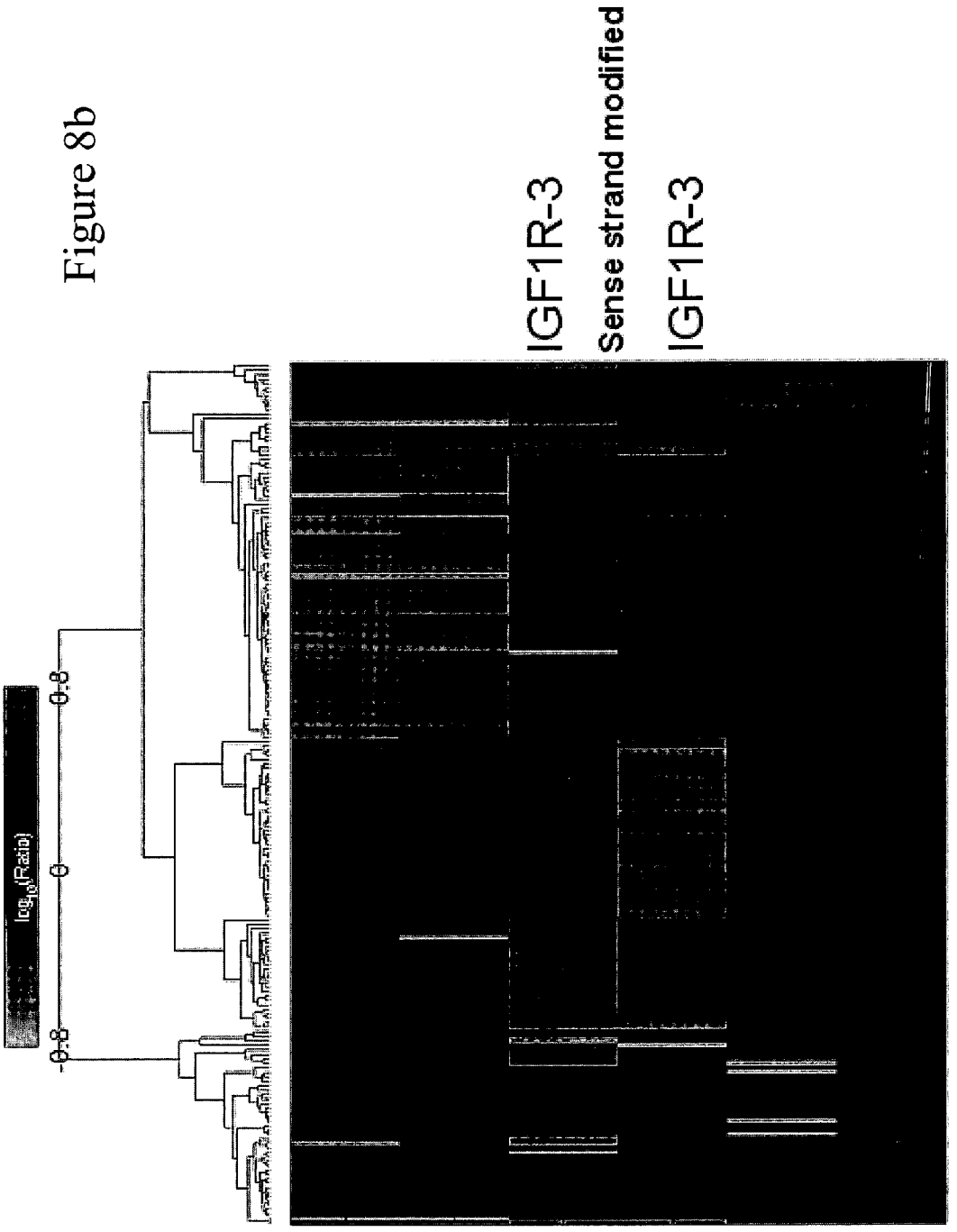

TARGET Screen Normalized LUC ASSAY 293 cells
LUC ASSAY/mock Ratio
1.2
1
0.8
0.6
0.4
0.2
0
siRNA 100nM
luc 56
luc 58
luc 63
luc 8
luc 81
S-AS
S-AS2M
S-5'pAS2M
S2M-AS
S2M-AS2M
S2M-5'pAS2M
MOPS Control

Figure 8a

Figure 8b



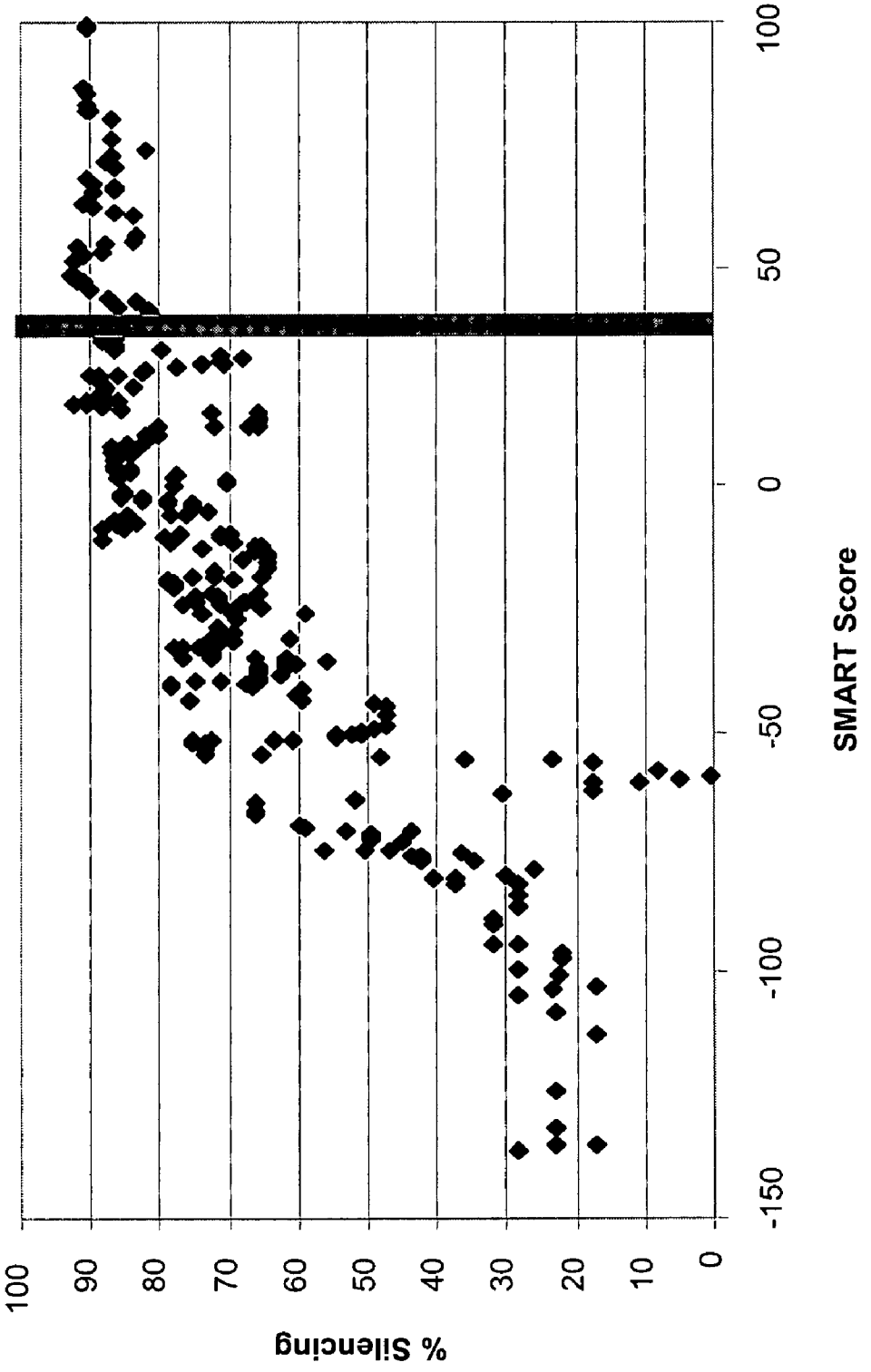

% Silencing
100
90
80
70
60
50
40
30
20
10
0
SMART Score
100
50
0
-50
-100
-150

Figure 9

Figure 10a

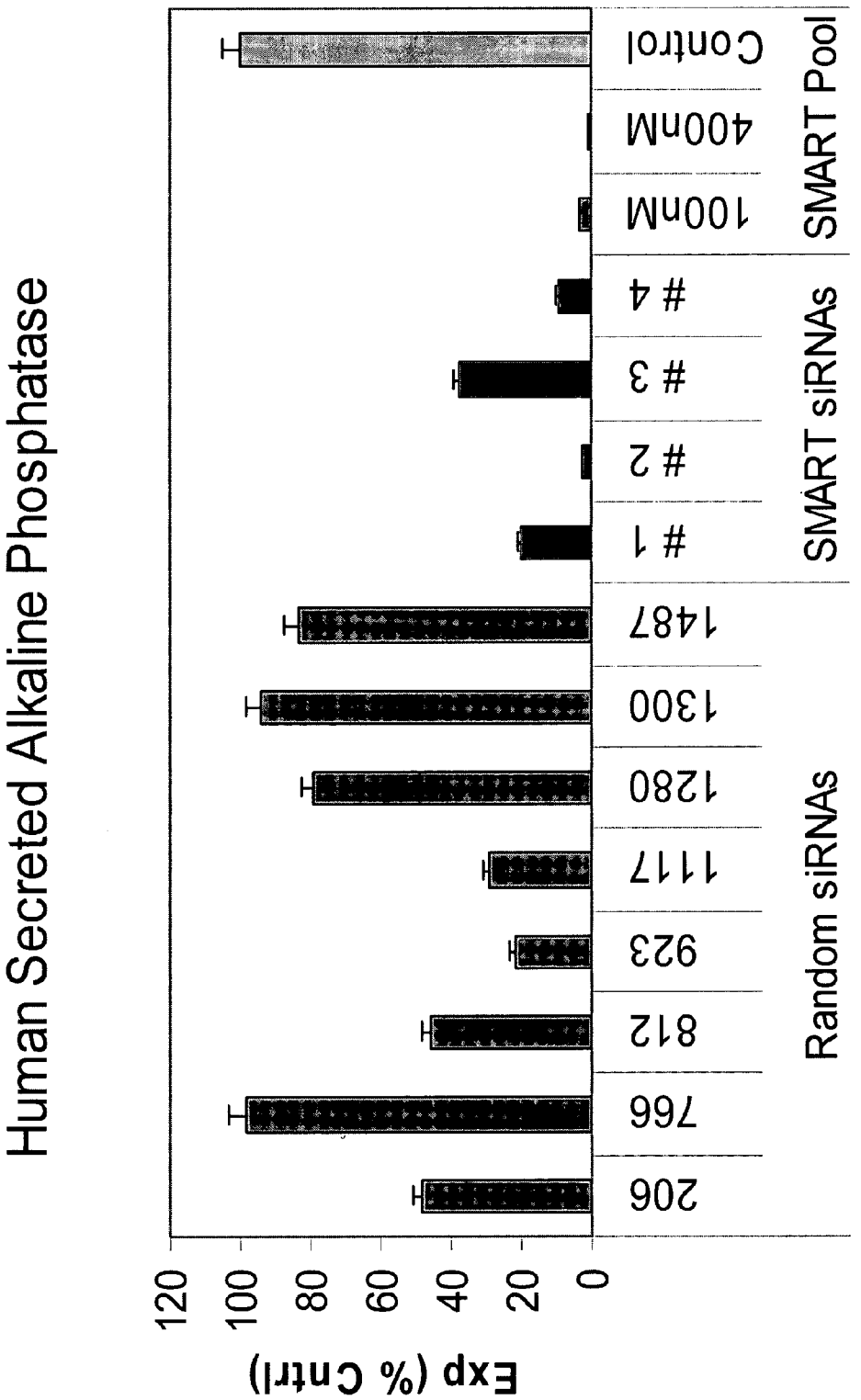

Human Secreted Alkaline Phosphatase
Exp (% Cntrl)
120
100
80
60
40
20
0
206
766
812
923
1117
1280
1300
1487
1
2
3
4
100nM
400nM
Control
Random siRNAs
SMART siRNAs
SMART Pool

Figure 10b

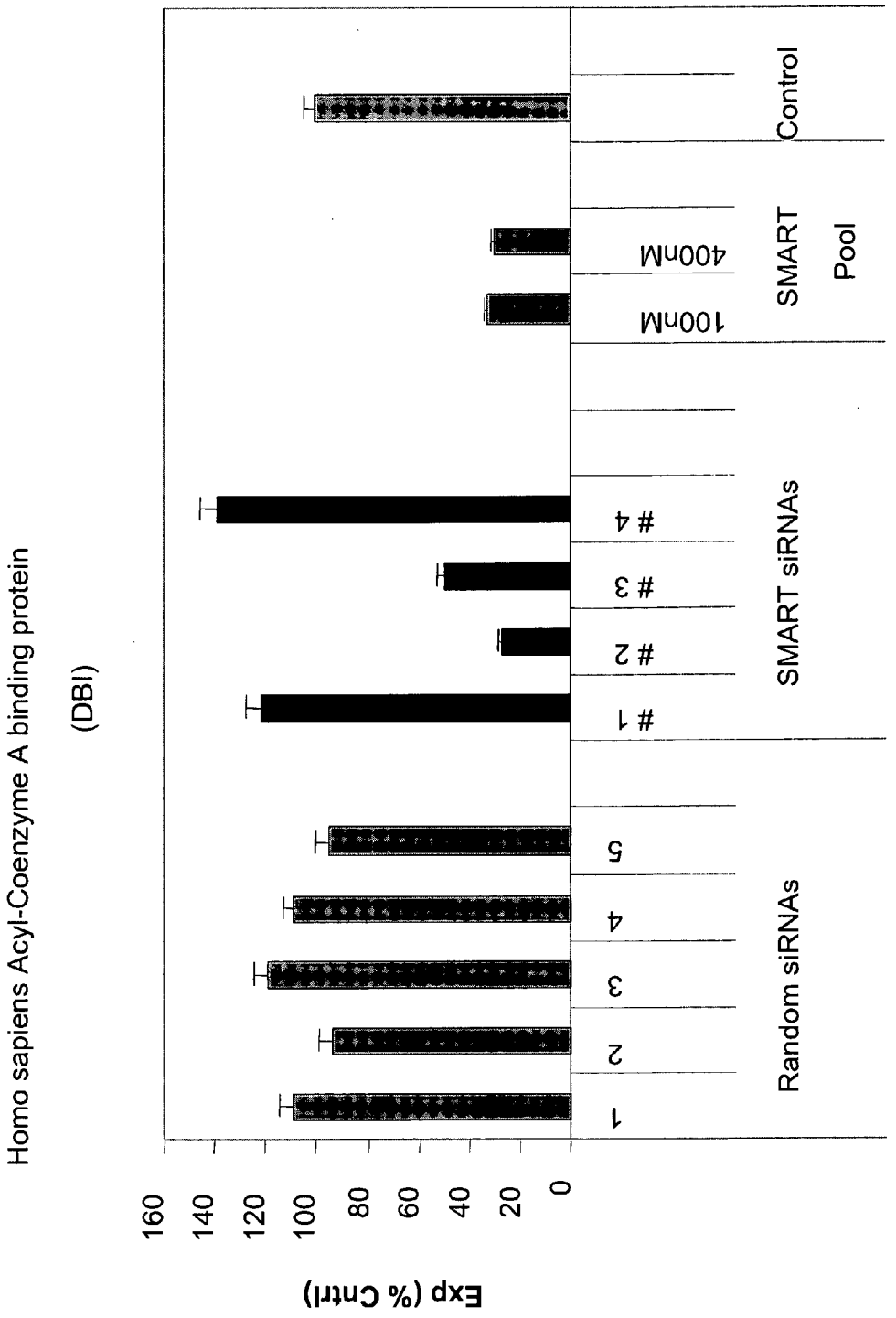

Homo sapiens Acyl-Coenzyme A binding protein
(DBI)
Exp (% Cntrl)
160
140
120
100
80
60
40
20
0
1
2
3
4
5
Random siRNAs
#1
#2
#3
#4
SMART siRNAs
100nM
400nM
SMART
Pool
Control

Figure 10e

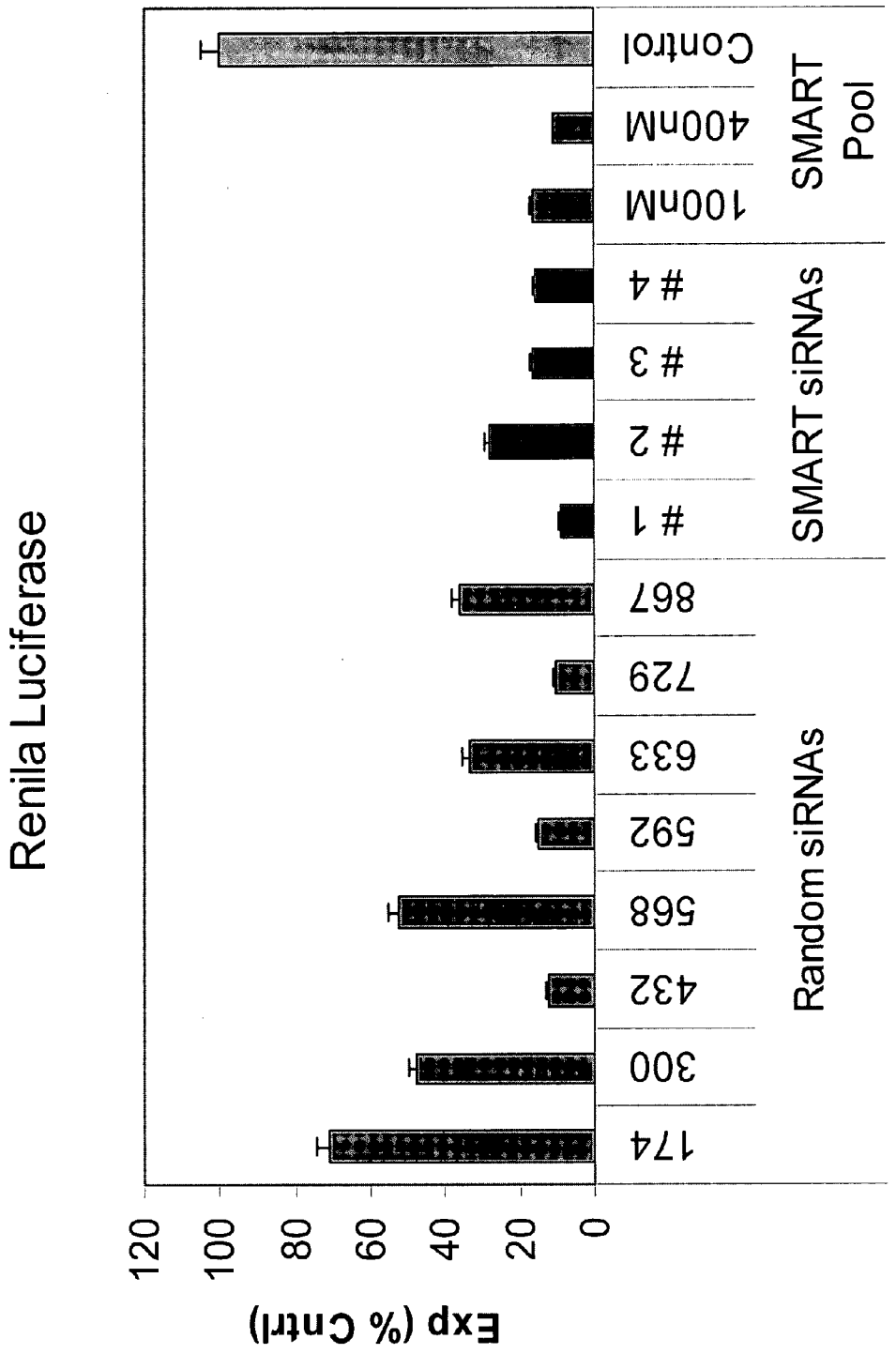

Renila Luciferase
Exp (% Cntrl)
120
100
80
60
40
20
0
174
300
432
568
592
633
729
867
1
2
3
4
100nM
400nM
Control
Random siRNAs
SMART siRNAs
SMART Pool

Figure 10d

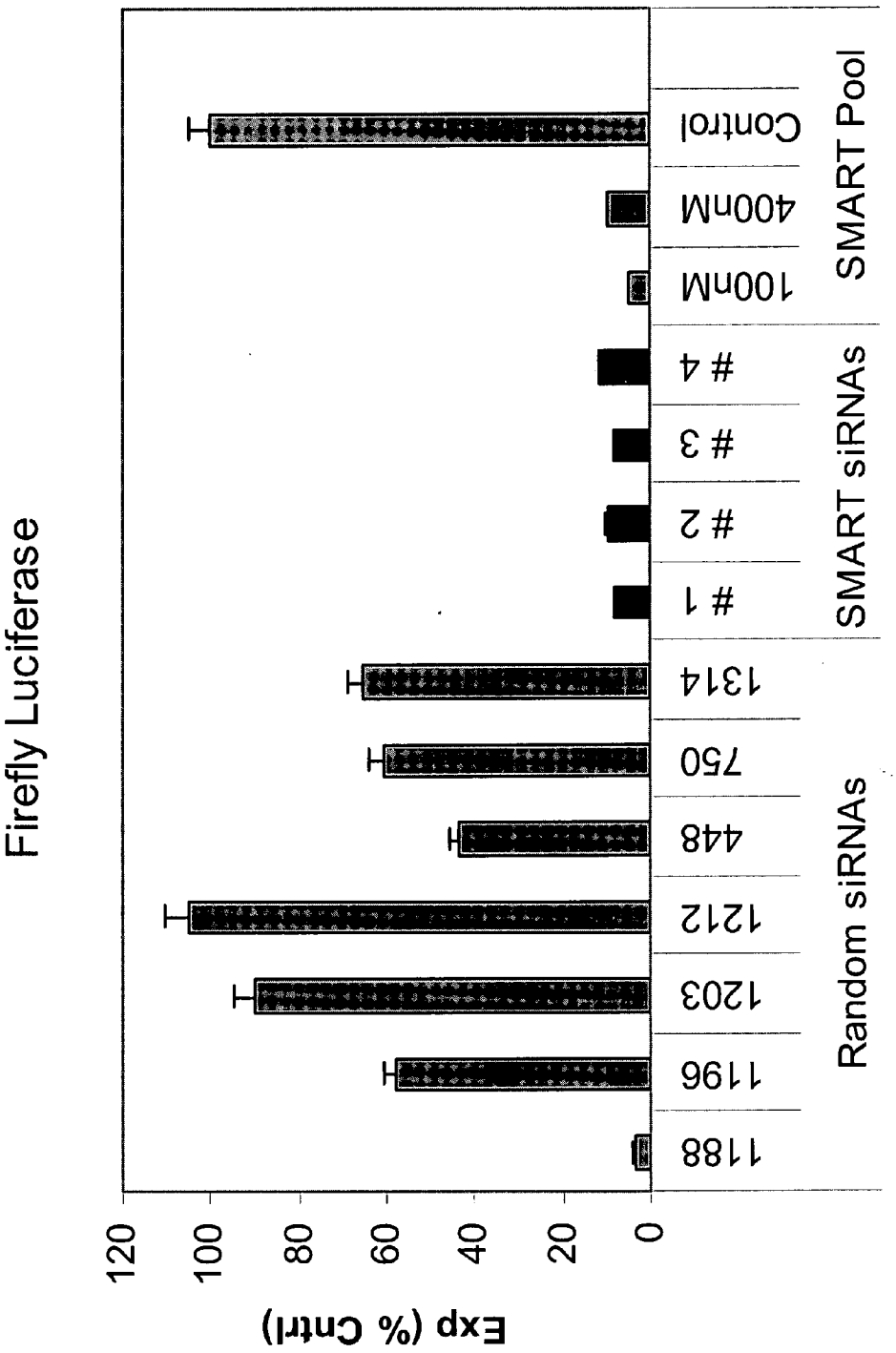

Firefly Luciferase
Exp (% Cntrl)
120
100
80
60
40
20
0
1188
1196
1203
1212
448
750
1314
1
2
3
4
100nM
400nM
Control
Random siRNAs
SMART siRNAs
SMART Pool

Figure 10e

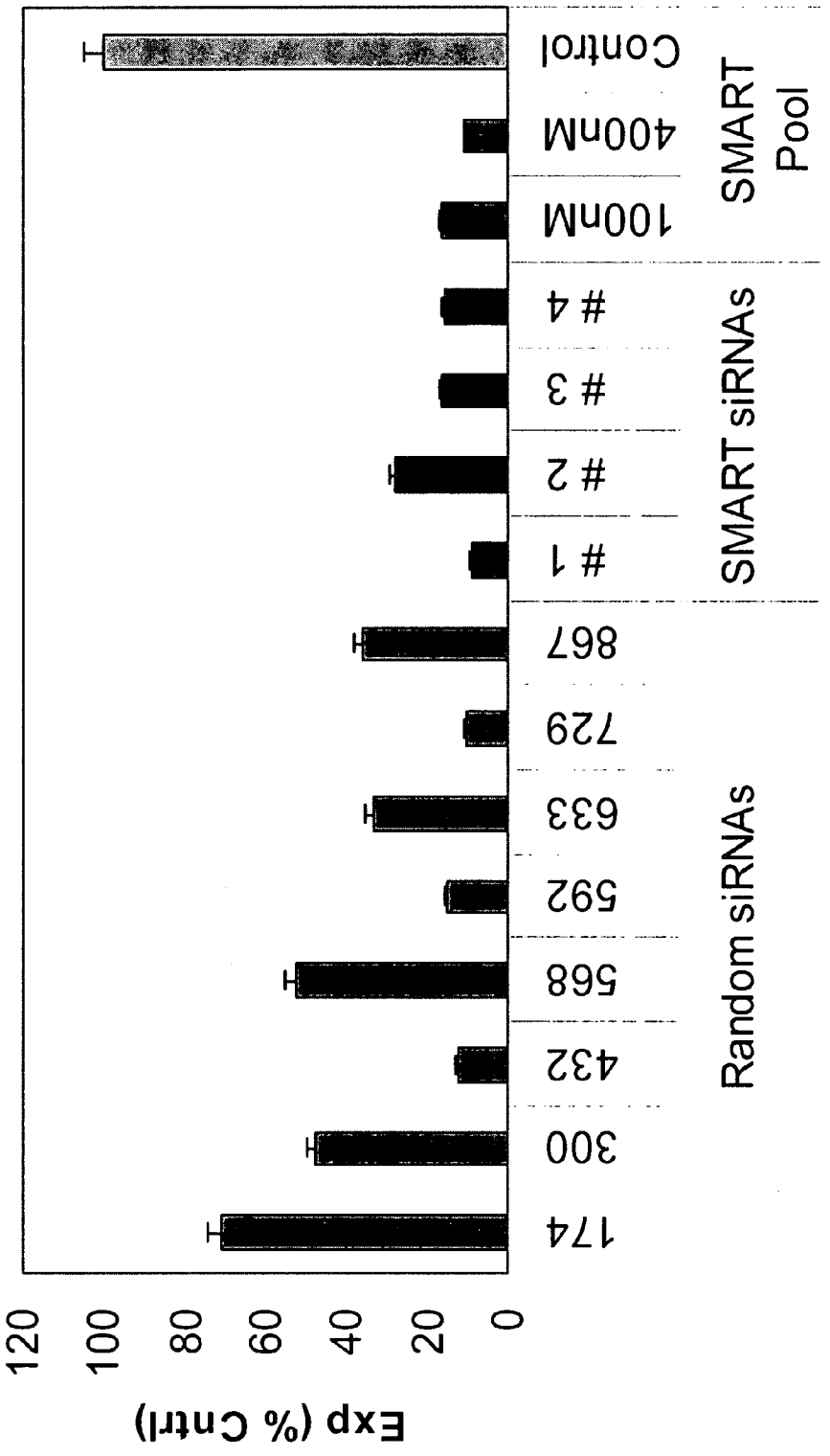

Renila Luciferase
Exp (% Cntrl)
120
100
80
60
40
20
0
174
300
432
568
592
633
729
867
1
2
3
4
100nM
400nM
Control
Random siRNAs
SMART siRNAs
SMART Pool

Figure 10f

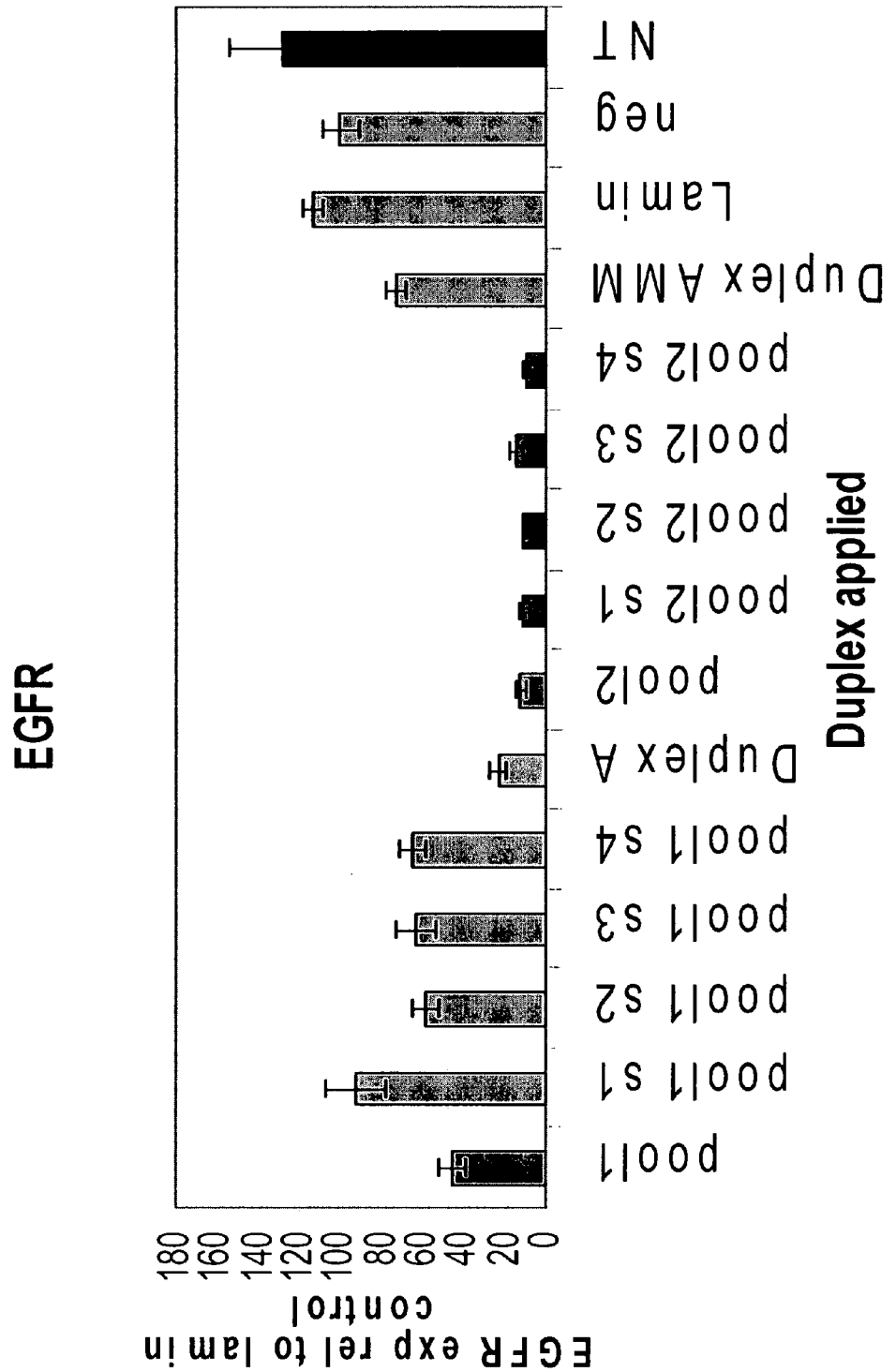

EGFR
EGFR exp rel to lamin control
0
20
40
60
80
100
120
140
160
180
Duplex applied
pool1
pool1 s1
pool1 s2
pool1 s3
pool1 s4
Duplex A
pool2
pool2 s1
pool2 s2
pool2 s3
pool2 s4
Duplex AMM
Lamin
neg
NT

Figure 11

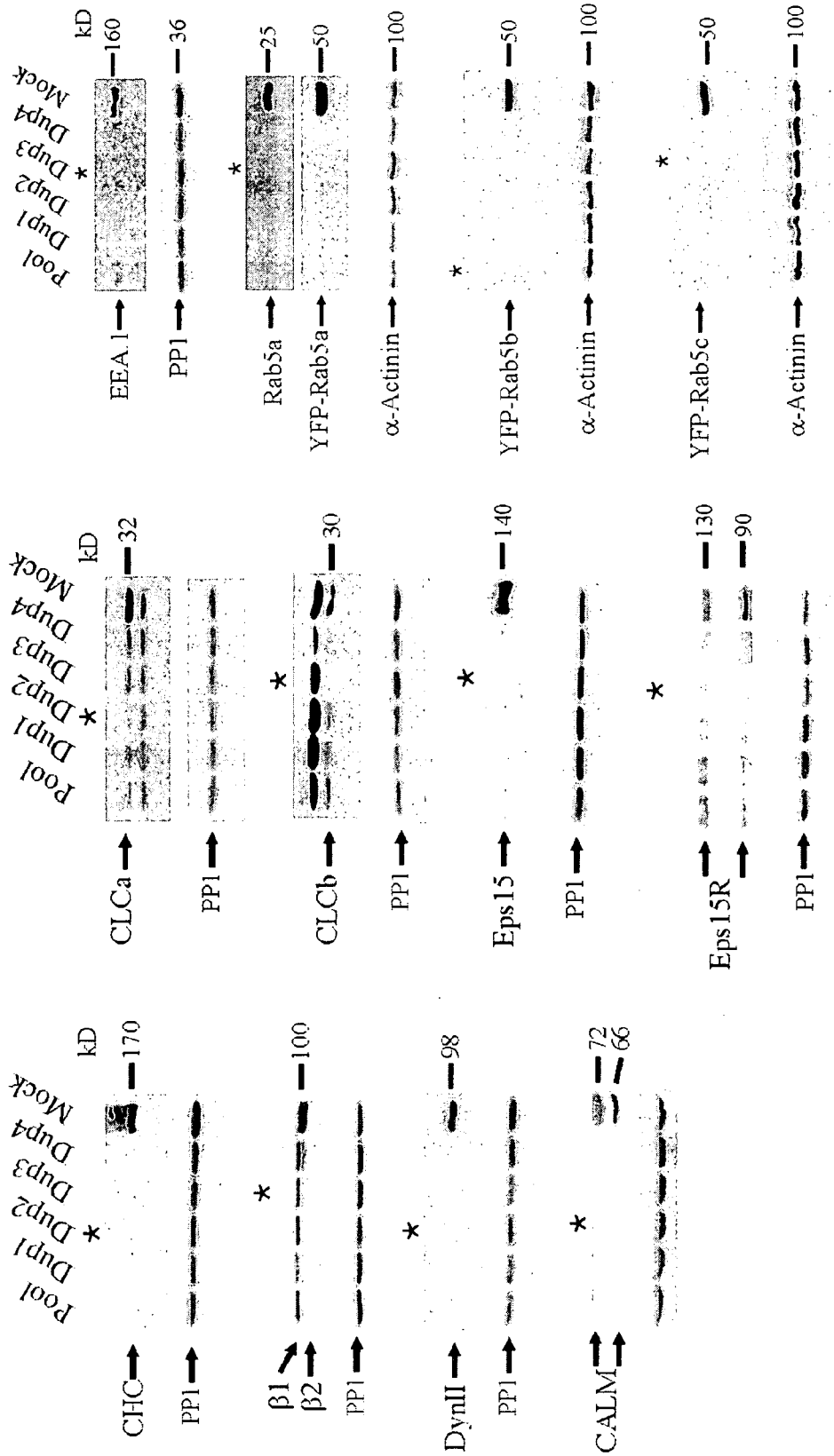

Pool
Dup1
Dup2
*
Dup3
Dup4
Mock
kD
CHC
170
PP1
β1
β2
100
PP1
DynII
98
PP1
CALM
72
66
CLCa
32
PP1
CLCb
30
PP1
Eps15
140
PP1
Eps15R
130
90
PP1
EEA1
160
PP1
36
Rab5a
25
YFP-Rab5a
50
α-Actinin
100
YFP-Rab5b
50
α-Actinin
100
YFP-Rab5c
50
α-Actinin
100

Figure 12

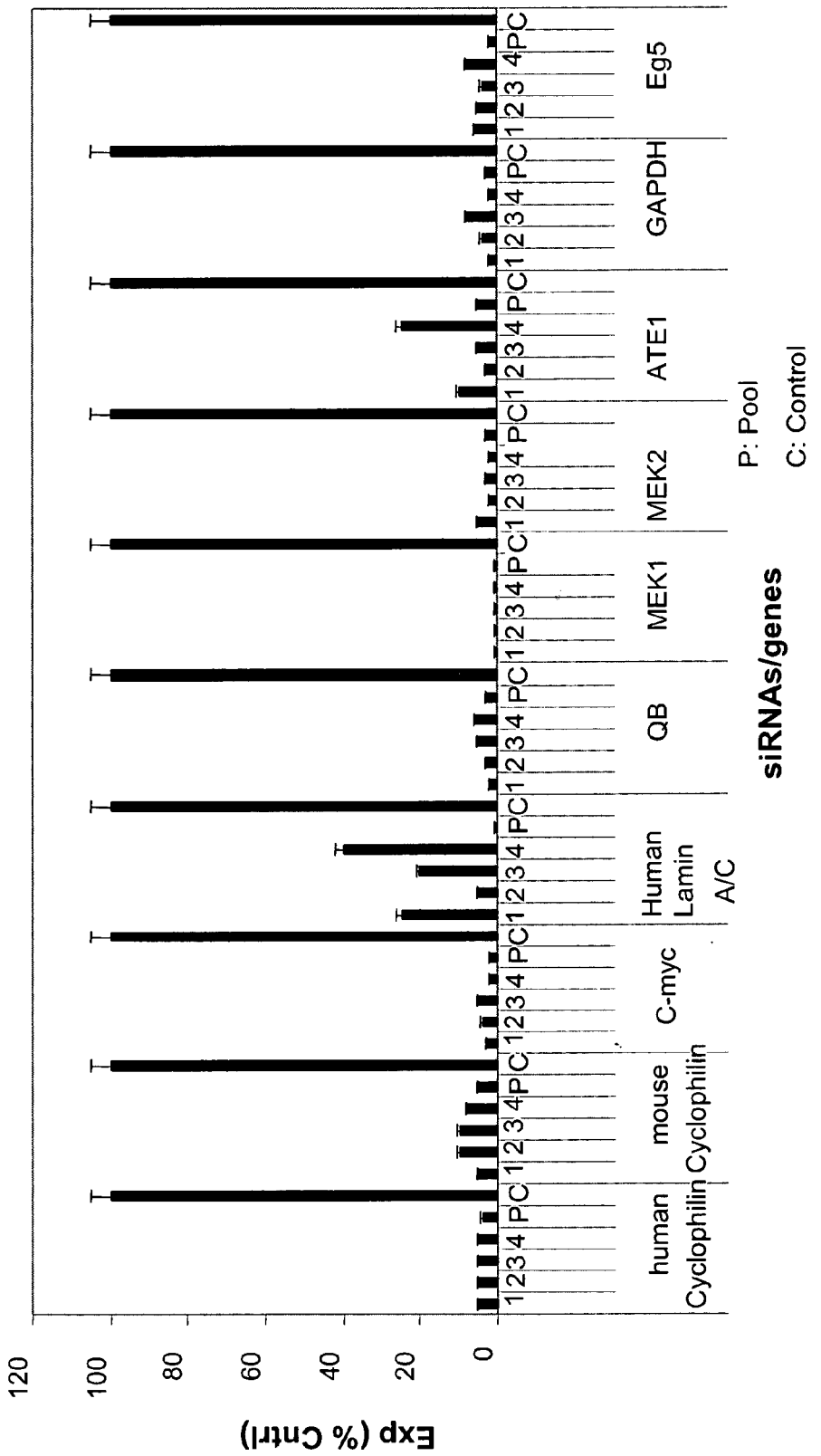
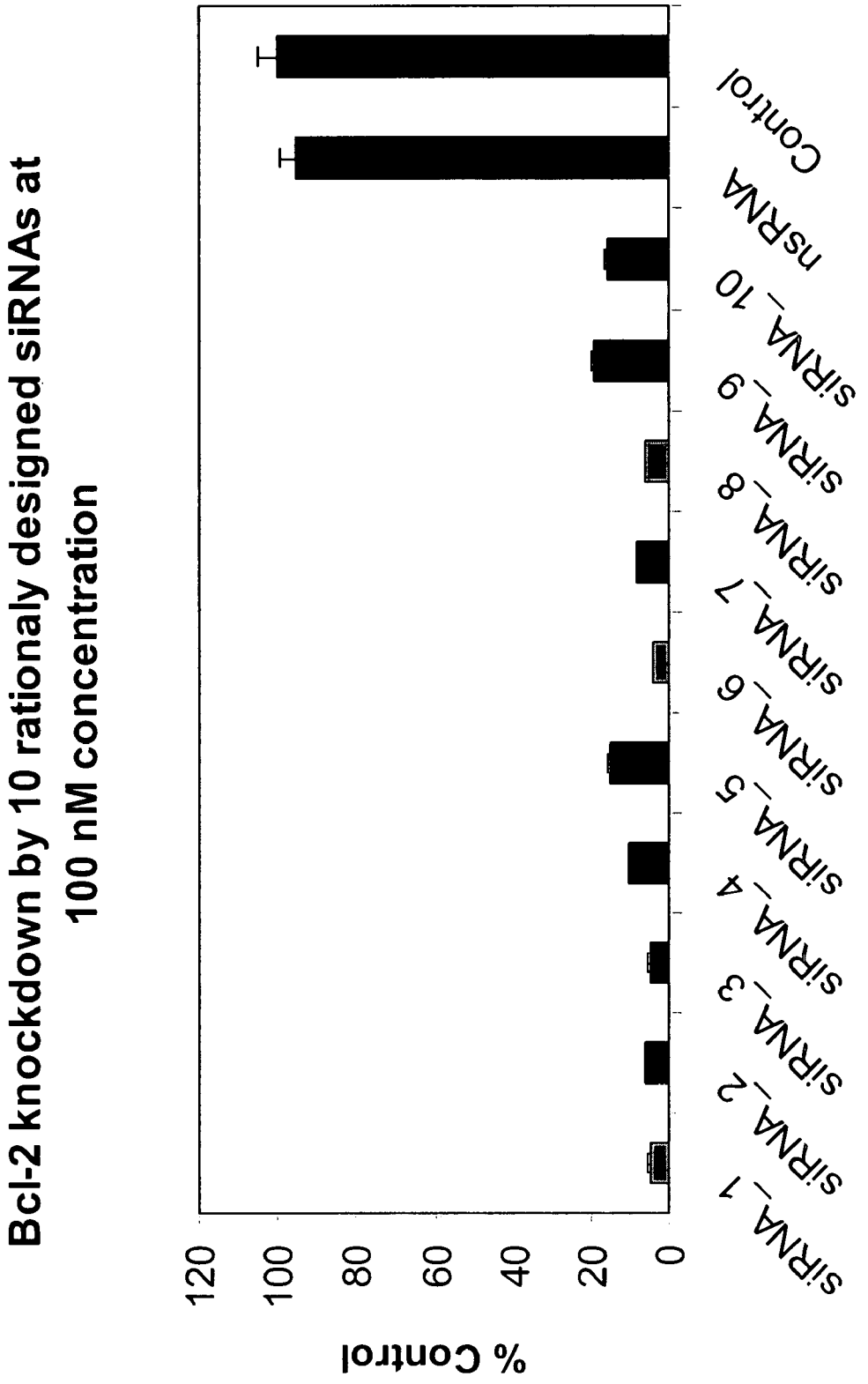

Rational selection validation
Exp (% Cntrl)
120
100
80
60
40
20
0
siRNAs/genes
human Cyclophilin
mouse Cyclophilin
C-myc
Human Lamin A/C
QB
MEK1
MEK2
ATE1
GAPDH
Eg5
1 2 3 4 PC
P: Pool
C: Control

Figure 13 Sequences of top Bcl2

siRNA 1 GGGAGAUAGUGAUGAAGUA (SEQ. ID NO. 302)
siRNA 2 GAAGUACAUCCAUUAUAAG (SEQ. ID NO. 303)
siRNA 3 GUACGACAACCGGGAGAUA (SEQ. ID NO. 304)
siRNA 4 AGAUAGUGAUGAAGUACAU (SEQ. ID NO. 305)
siRNA 5 UGAAGACUCUGCUCAGUUU (SEQ. ID NO. 306)
siRNA 6 GCAUGCGGCCUCUGUUUGA (SEQ. ID NO. 307)
siRNA 7 UGCGGCCUCUGUUUGAUUU (SEQ. ID NO. 308)
siRNA 8 GAGAUAGUGAUGAAGUACA (SEQ. ID NO. 309)
siRNA 9 GGAGAUAGUGAUGAAGUAC (SEQ. ID NO. 310)
siRNA 10 GAAGACUCUGCUCAGUUUG (SEQ. ID NO. 311)

Figure 14


Bcl-2 knockdown by 10 rationaly designed siRNAs at 100 nM concentration
% Control
120
100
80
60
40
20
0
siRNA_1
siRNA_2
siRNA_3
siRNA_4
siRNA_5
siRNA_6
siRNA_7
siRNA_8
siRNA_9
siRNA_10
nsRNA
Control

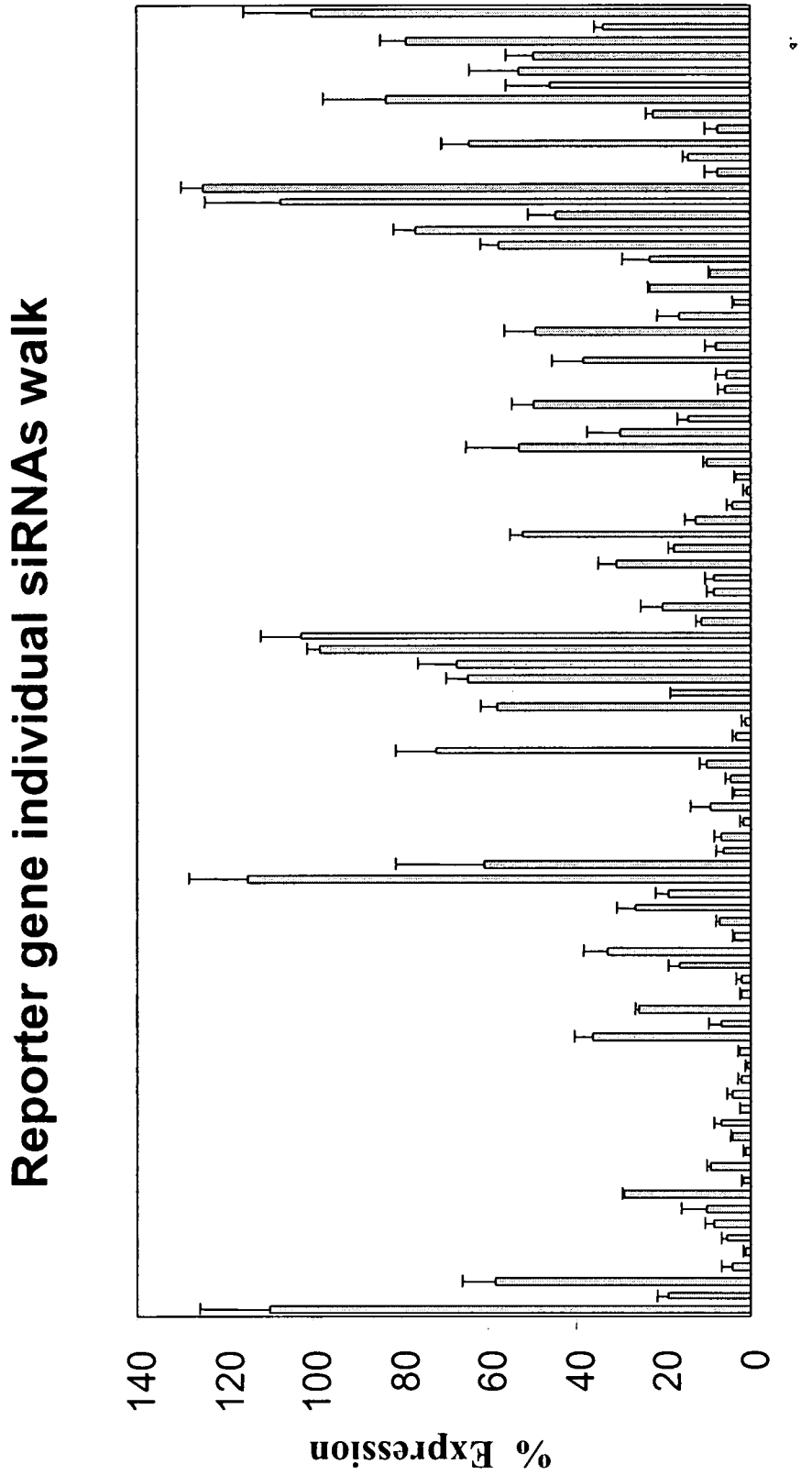
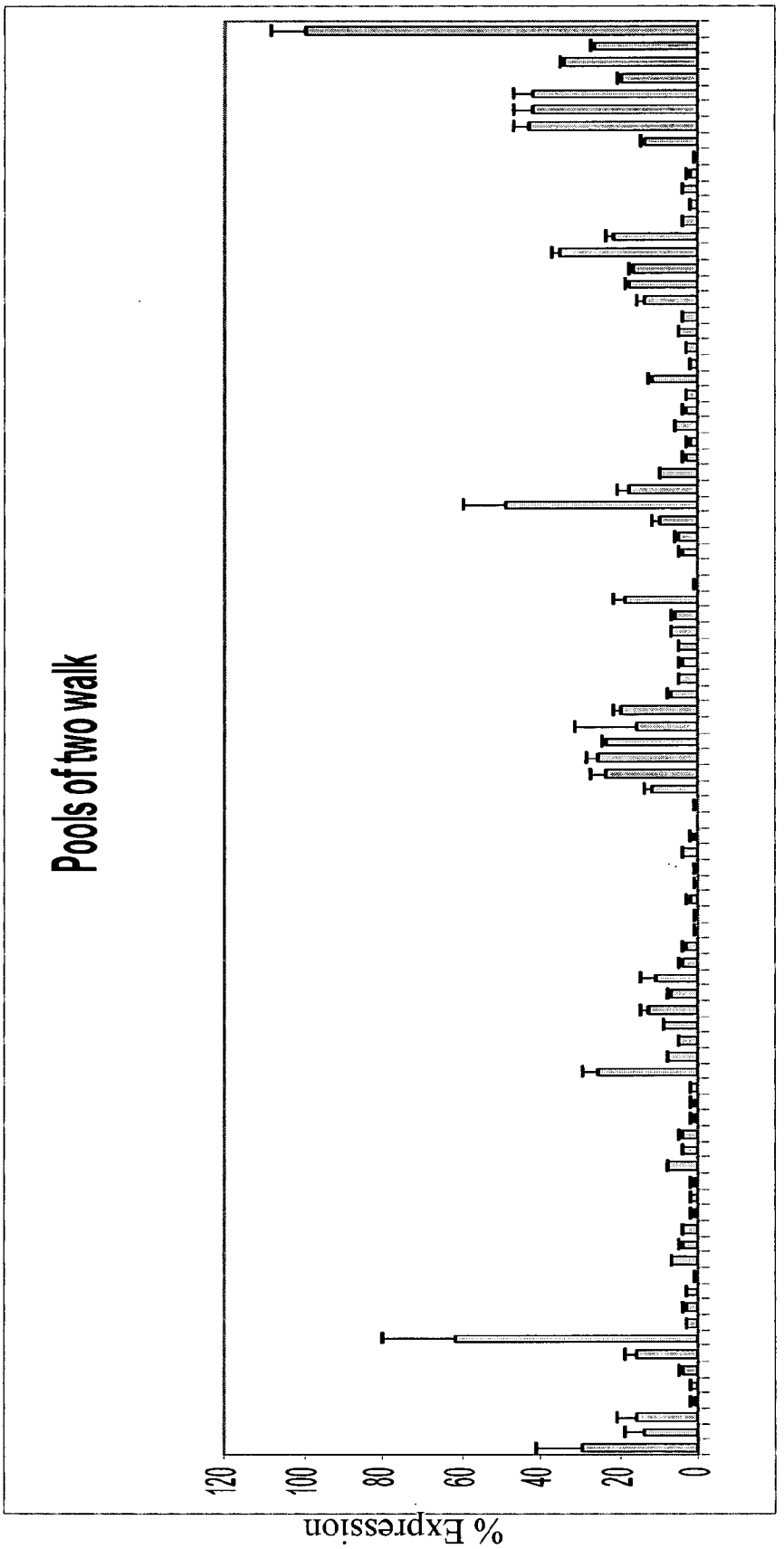

Reporter gene individual siRNAs walk
% Expression
140
120
100
80
60
40
20
0

Figure 15

Figure 16 A



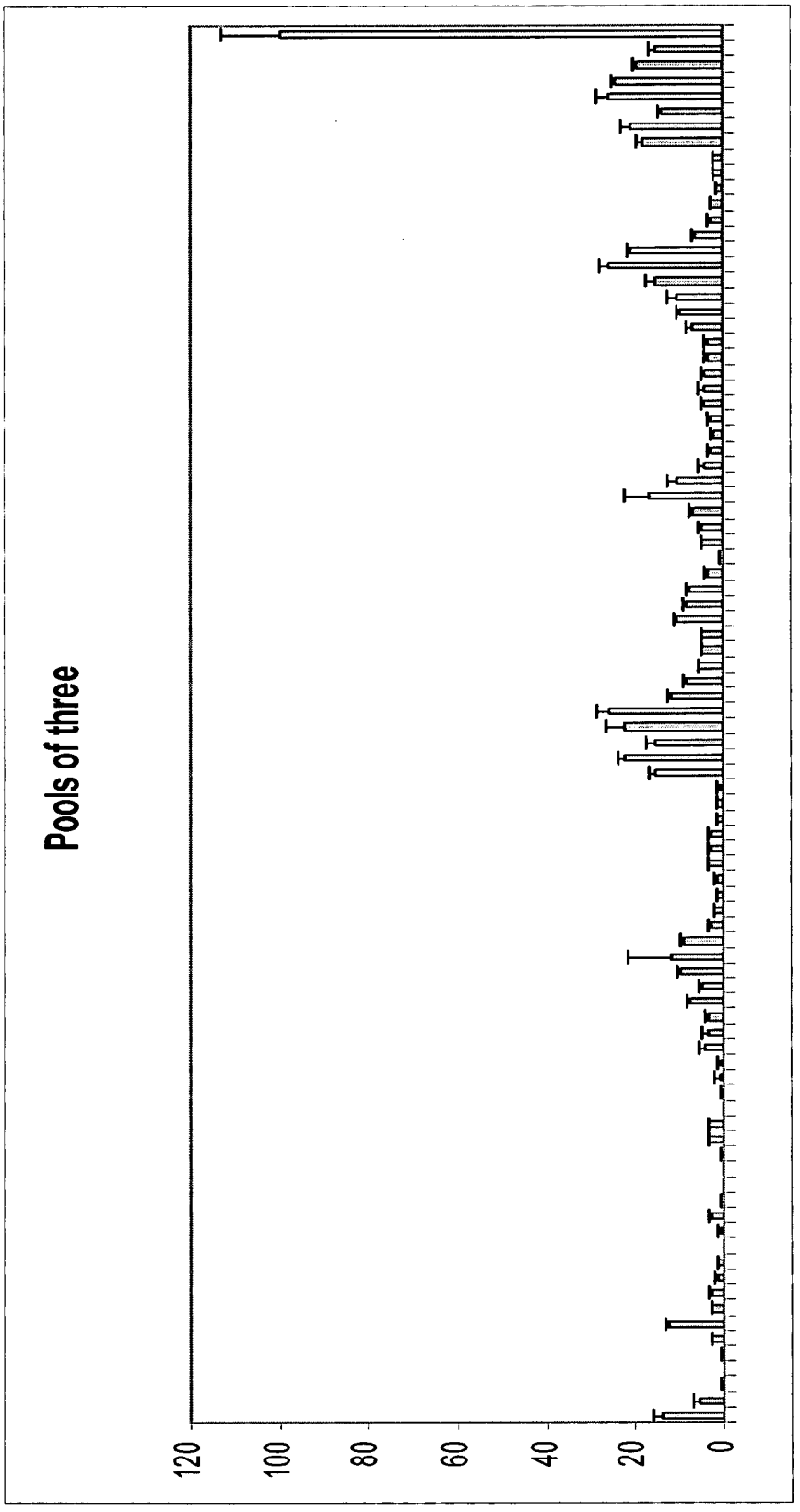


Figure 16 B

Figure 17 A

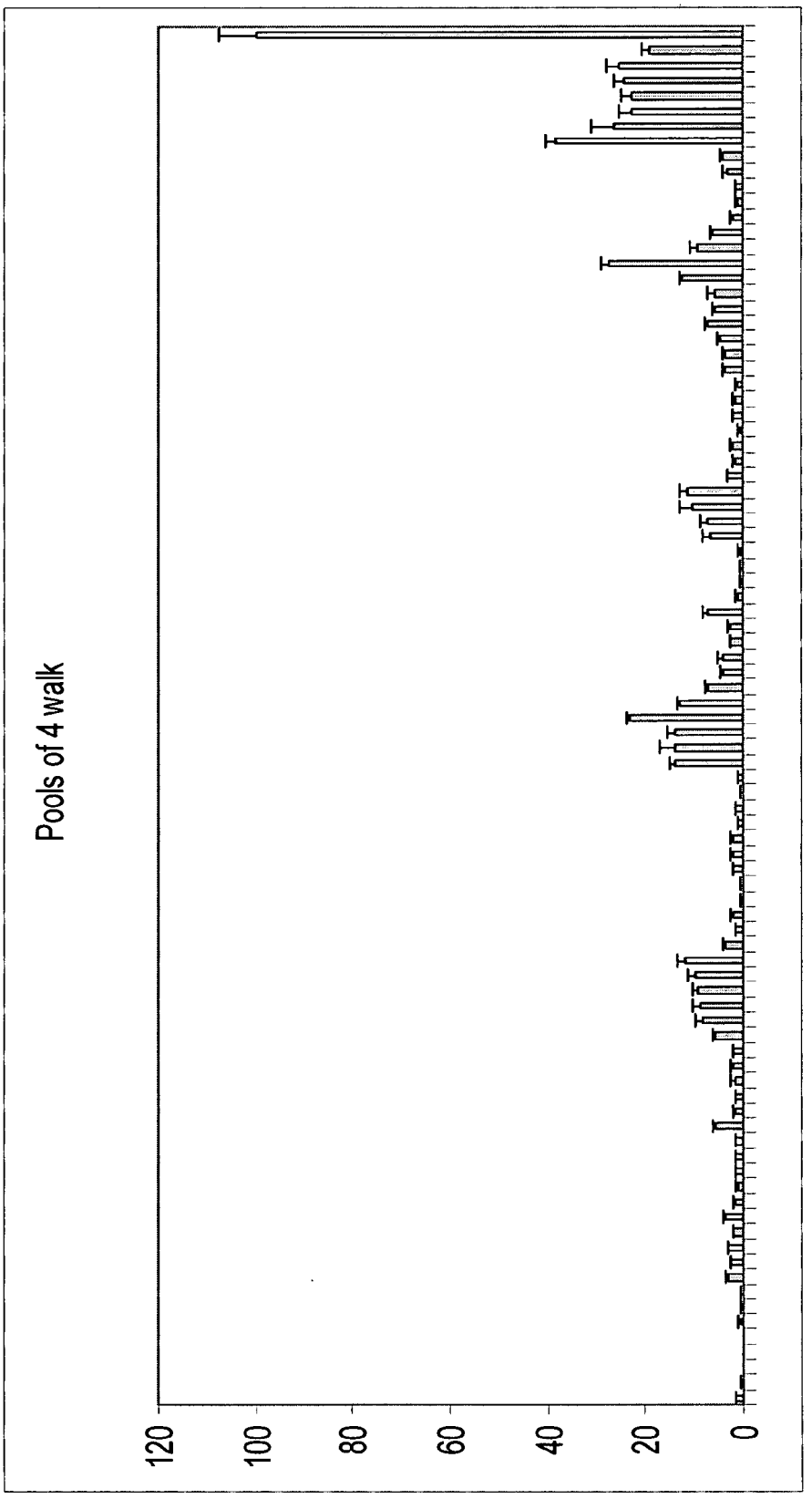


Figure 17 B

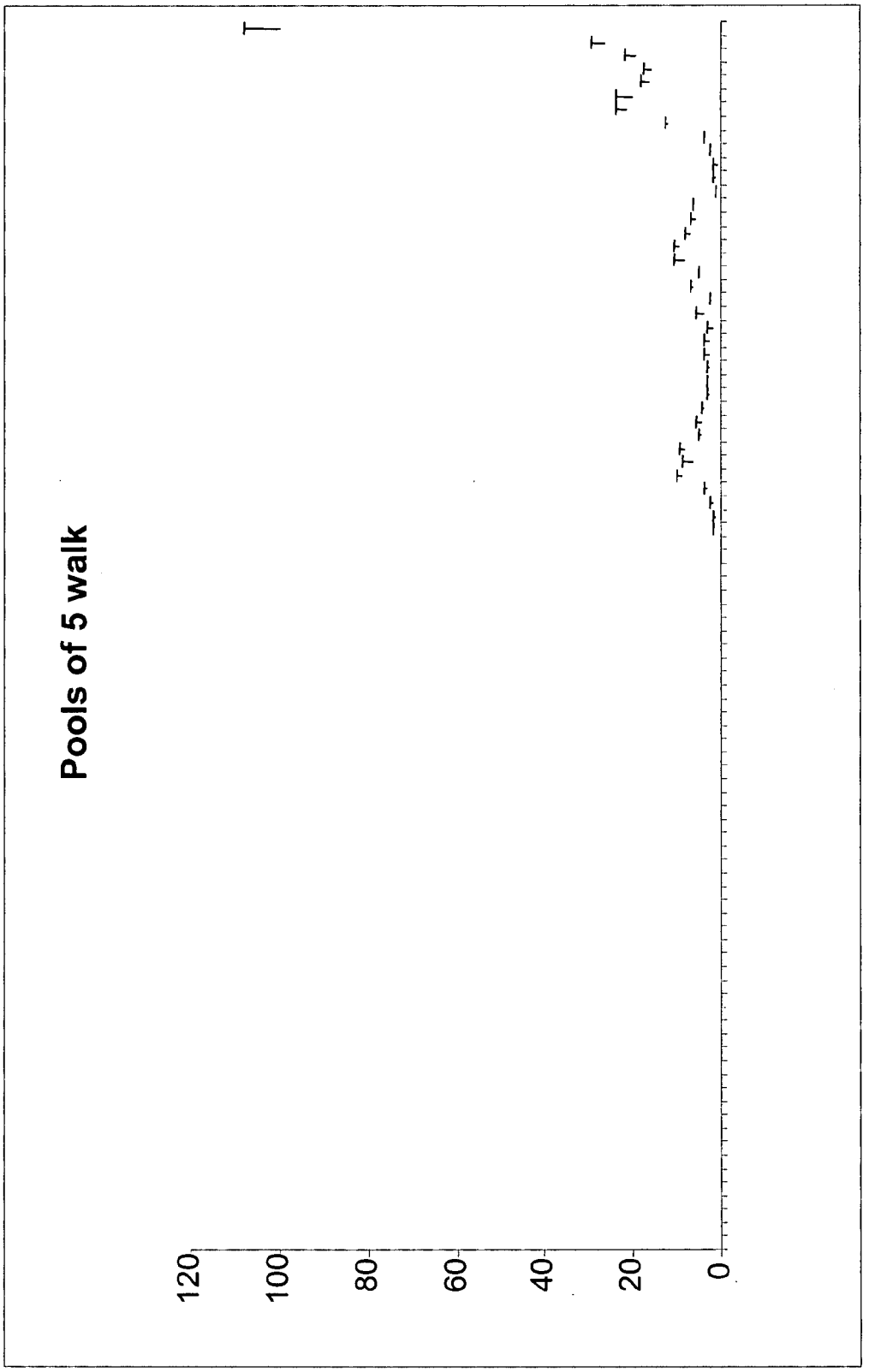
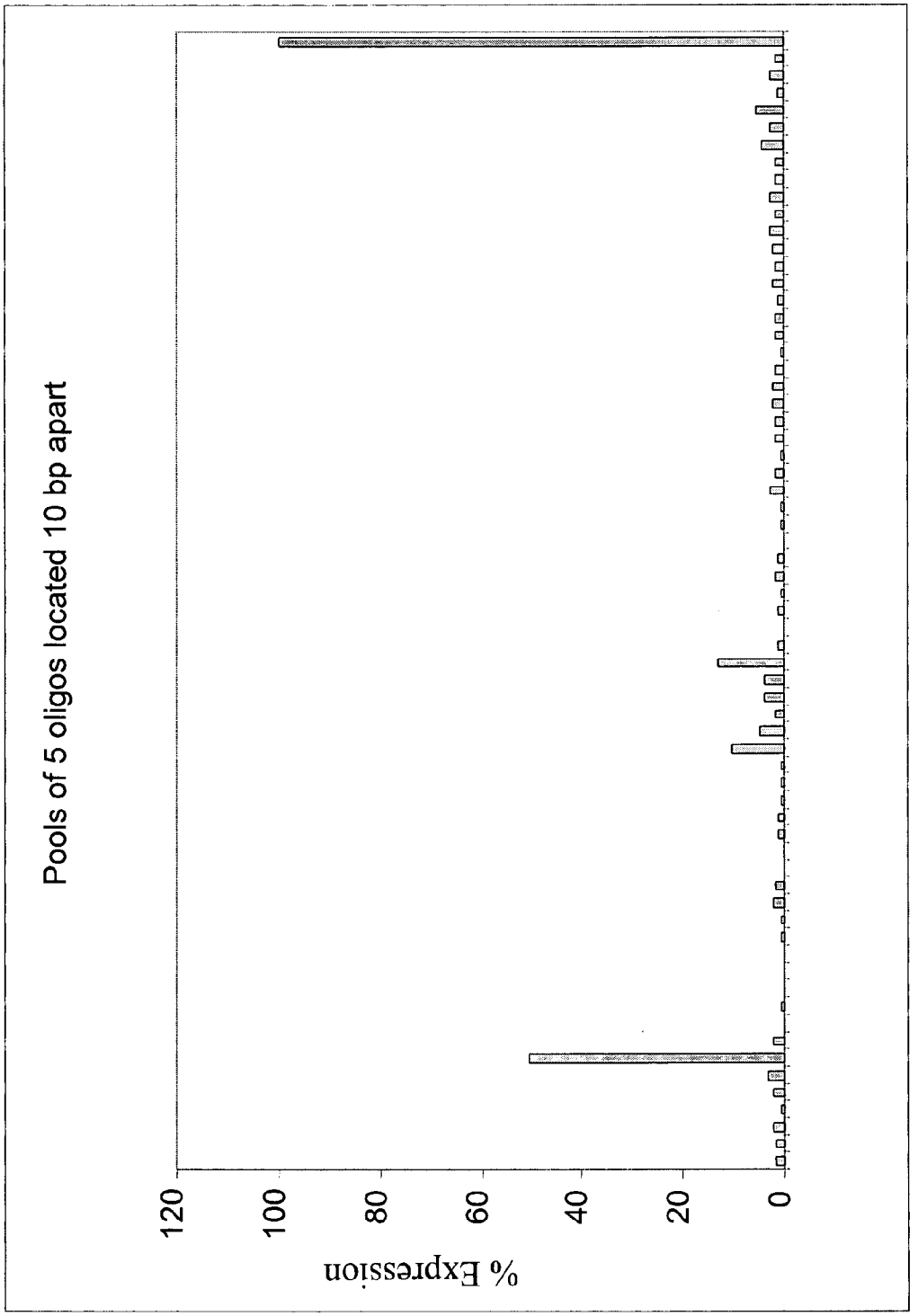


Figure 18 A


Pools of 5 oligos located 10 bp apart
% Expression
120
100
80
60
40
20
0

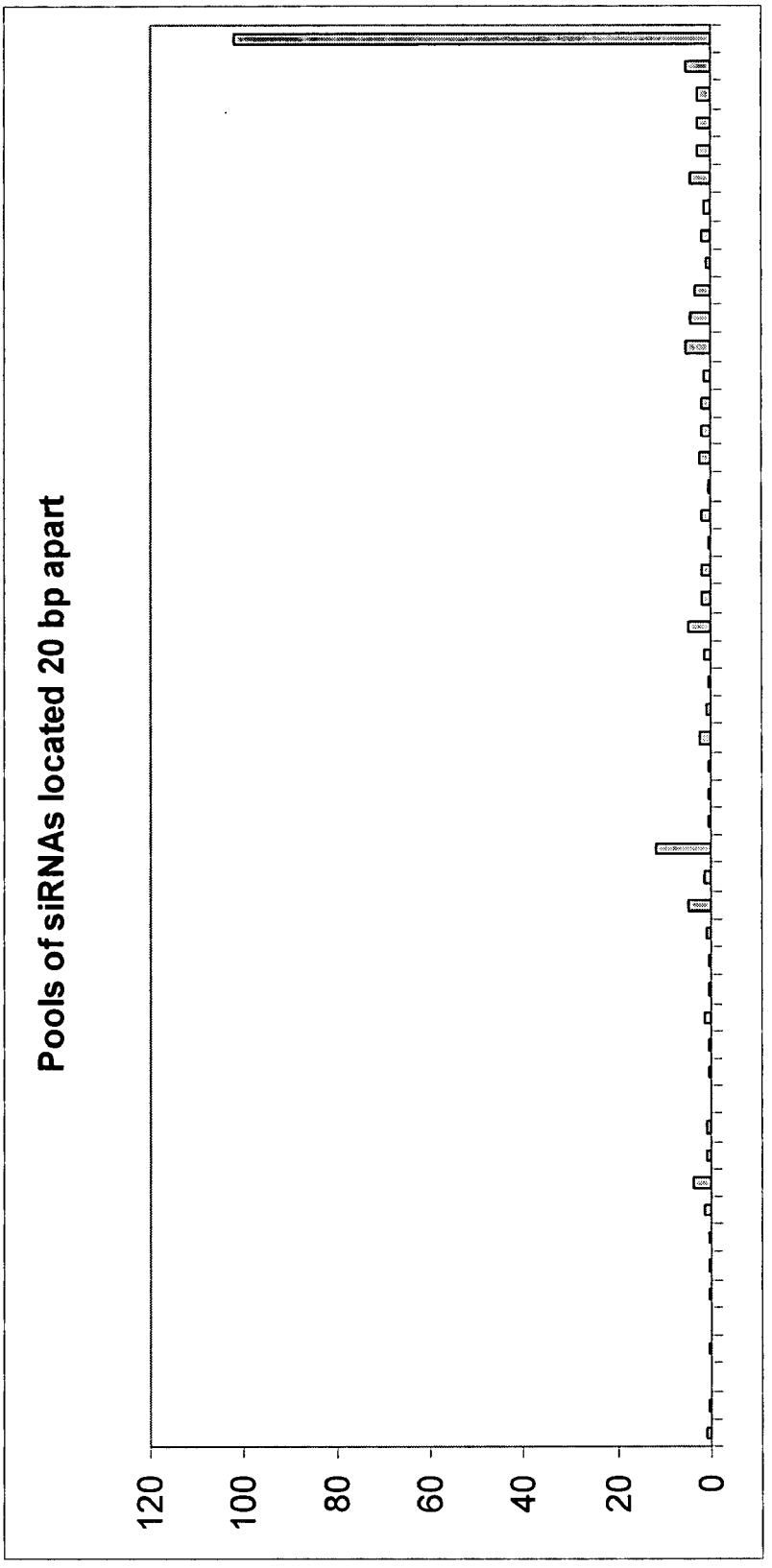

Pools of siRNAs located 20 bp apart
120
100
80
60
40
20
0
% Expression

Figure 18 B

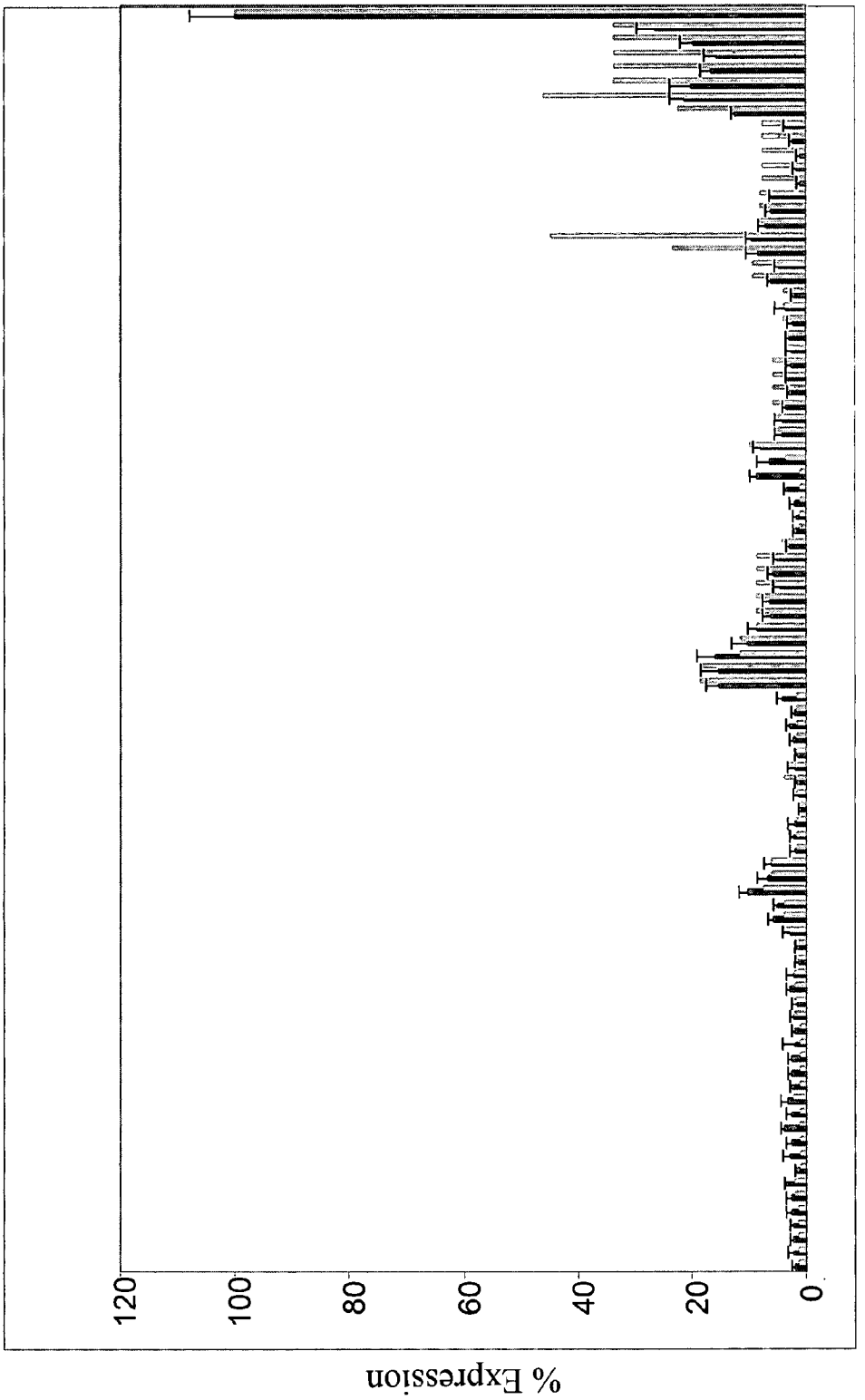


Figure 19

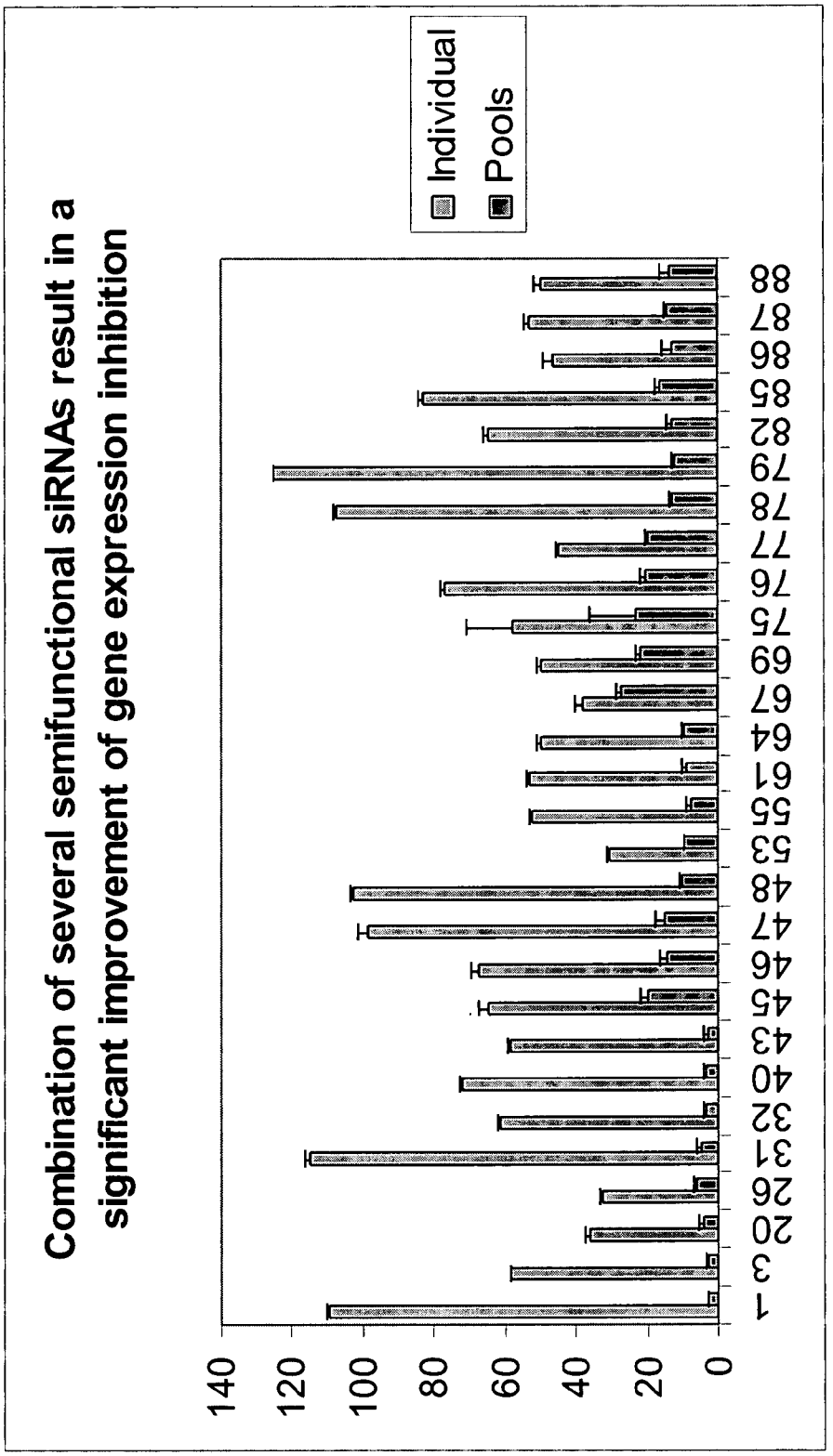

Combination of several semifunctional siRNAs result in a significant improvement of gene expression inhibition
Individual
Pools
% Expression
0
20
40
60
80
100
120
140
1
3
20
26
31
32
40
43
45
46
47
48
53
55
61
64
67
69
75
76
77
78
79
82
85
86
87
88

Figure 20

Figure 21A

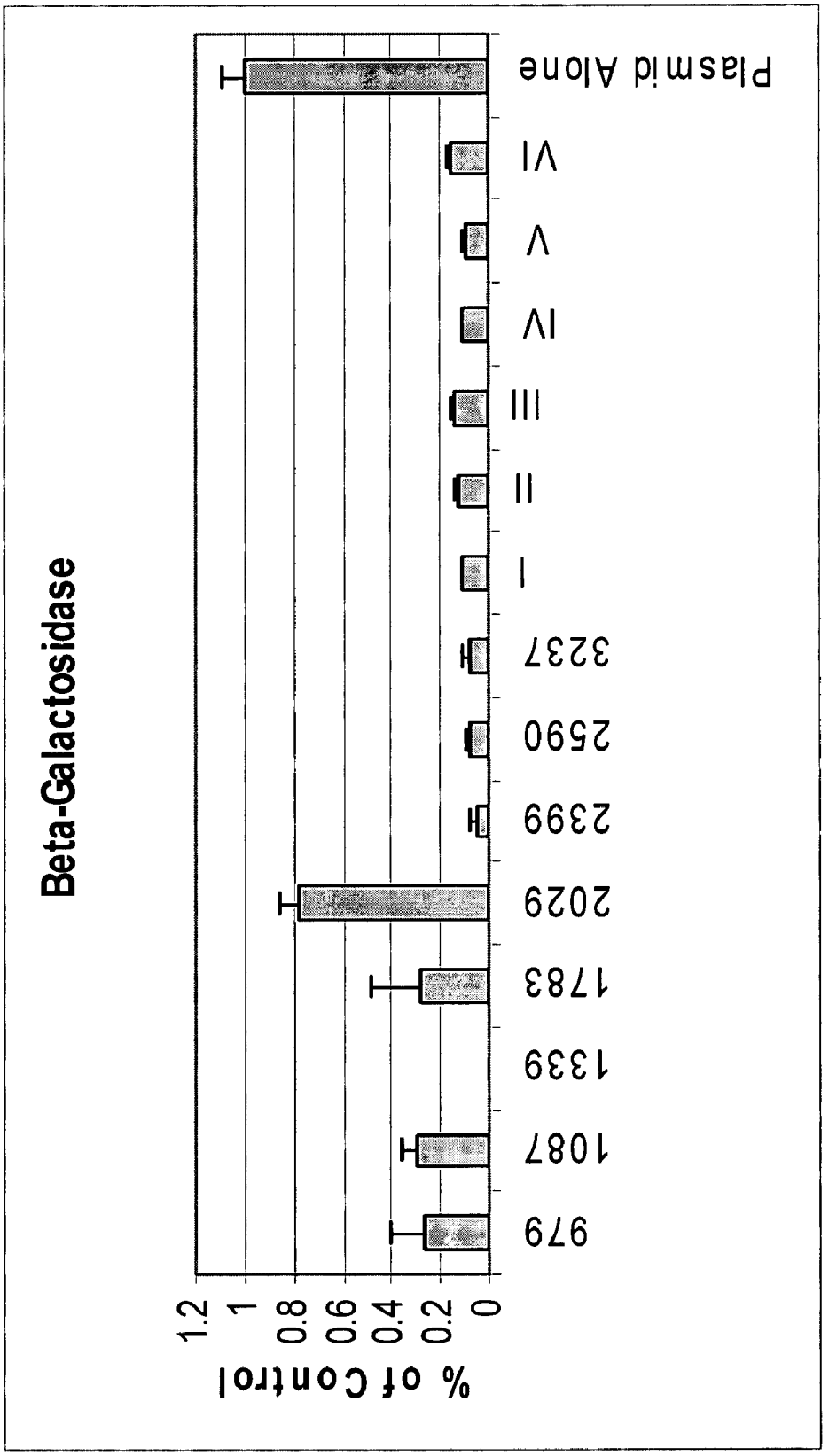
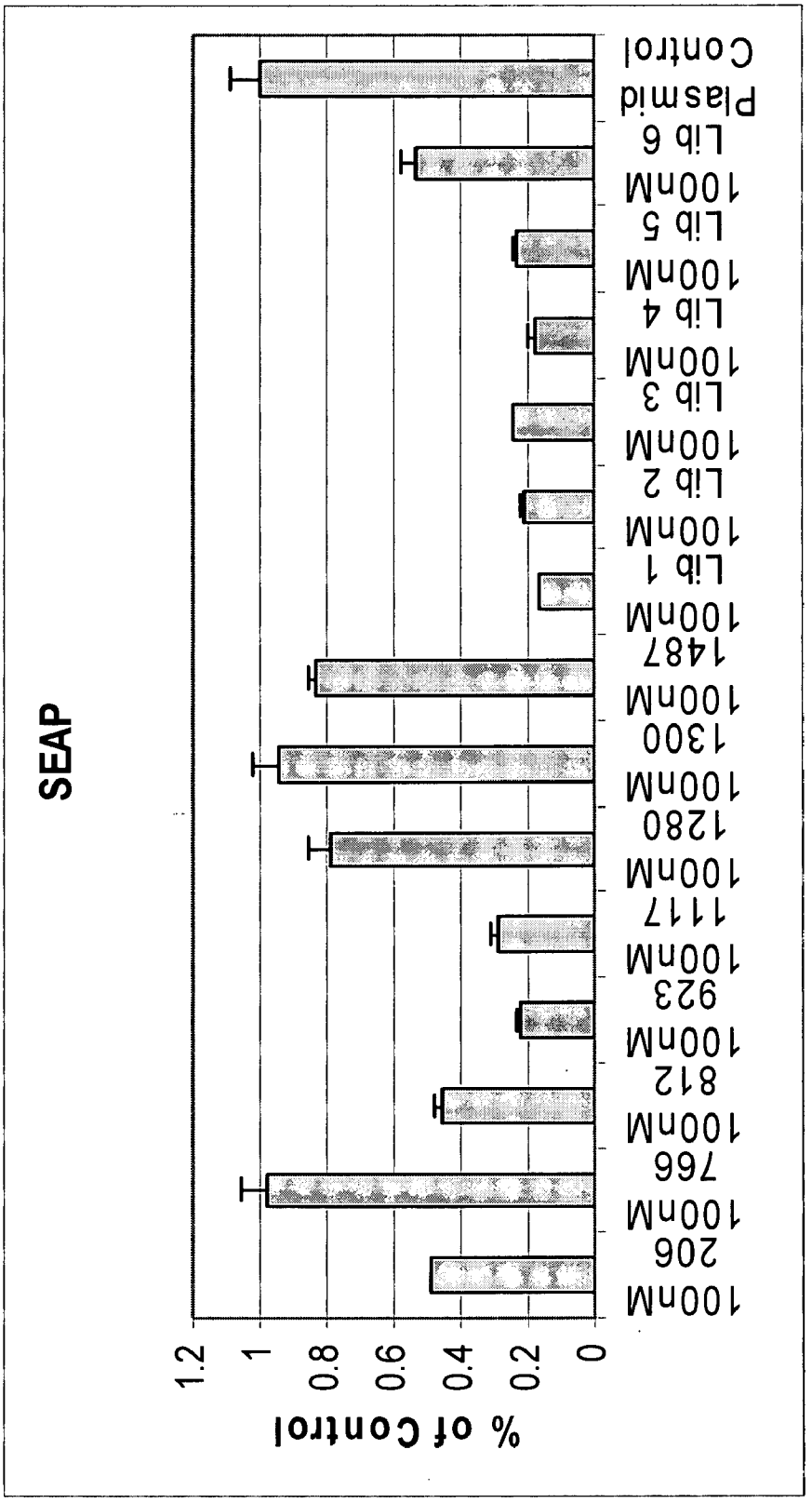

Beta-Galactosidase
% of Control
1.2
1
0.8
0.6
0.4
0.2
0
979
1087
1339
1783
2029
2399
2590
3237
I
II
III
IV
V
VI
Plasmid Alone

Figure 21B


SEAP
% of Control
1.2
1
0.8
0.6
0.4
0.2
0
100nM
206
100nM
766
100nM
812
100nM
923
100nM
1117
100nM
1280
100nM
1300
100nM
1487
100nM
Lib 1
100nM
Lib 2
100nM
Lib 3
100nM
Lib 4
100nM
Lib 5
100nM
Lib 6
Plasmid
Control

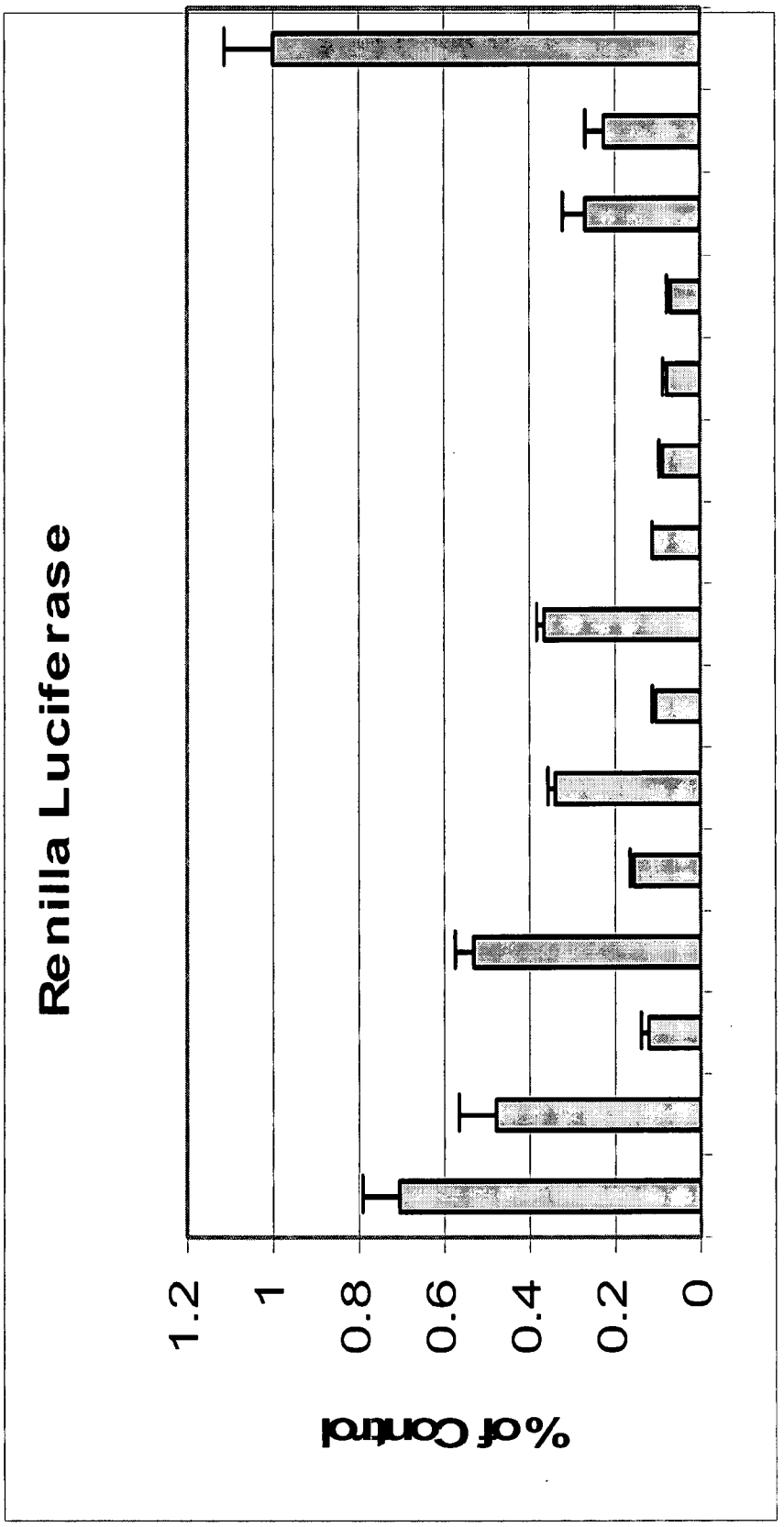


Figure 21C

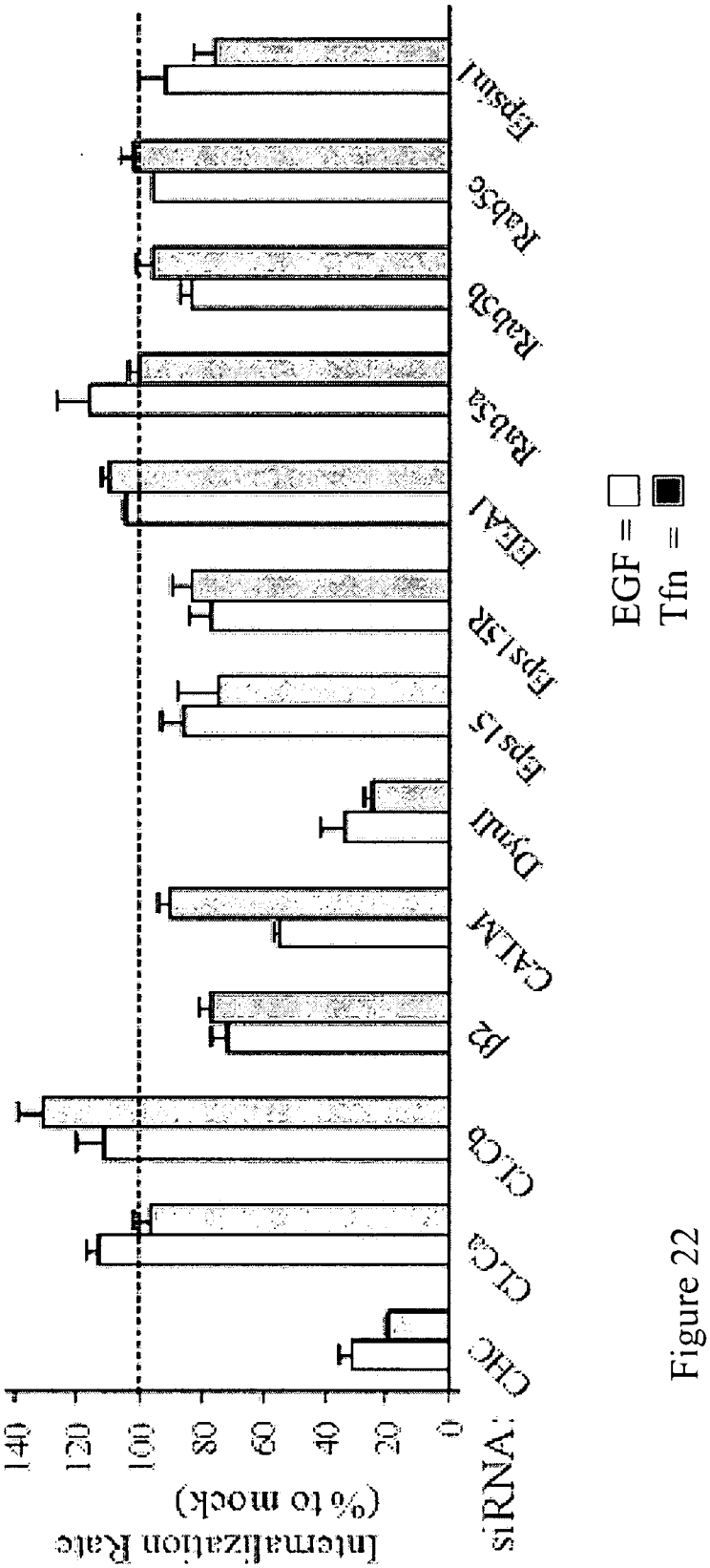

siRNA:
CHC
CLCa
CLCb
β2
CALM
Dynll
Eps15
Eps15R
EGAL
Rab5a
Rab5b
Rab5c
Epsin1
Internalization Rate
(% to mock)
0
20
40
60
80
100
120
140
EGF = □ ■
Tfn =

Figure 22

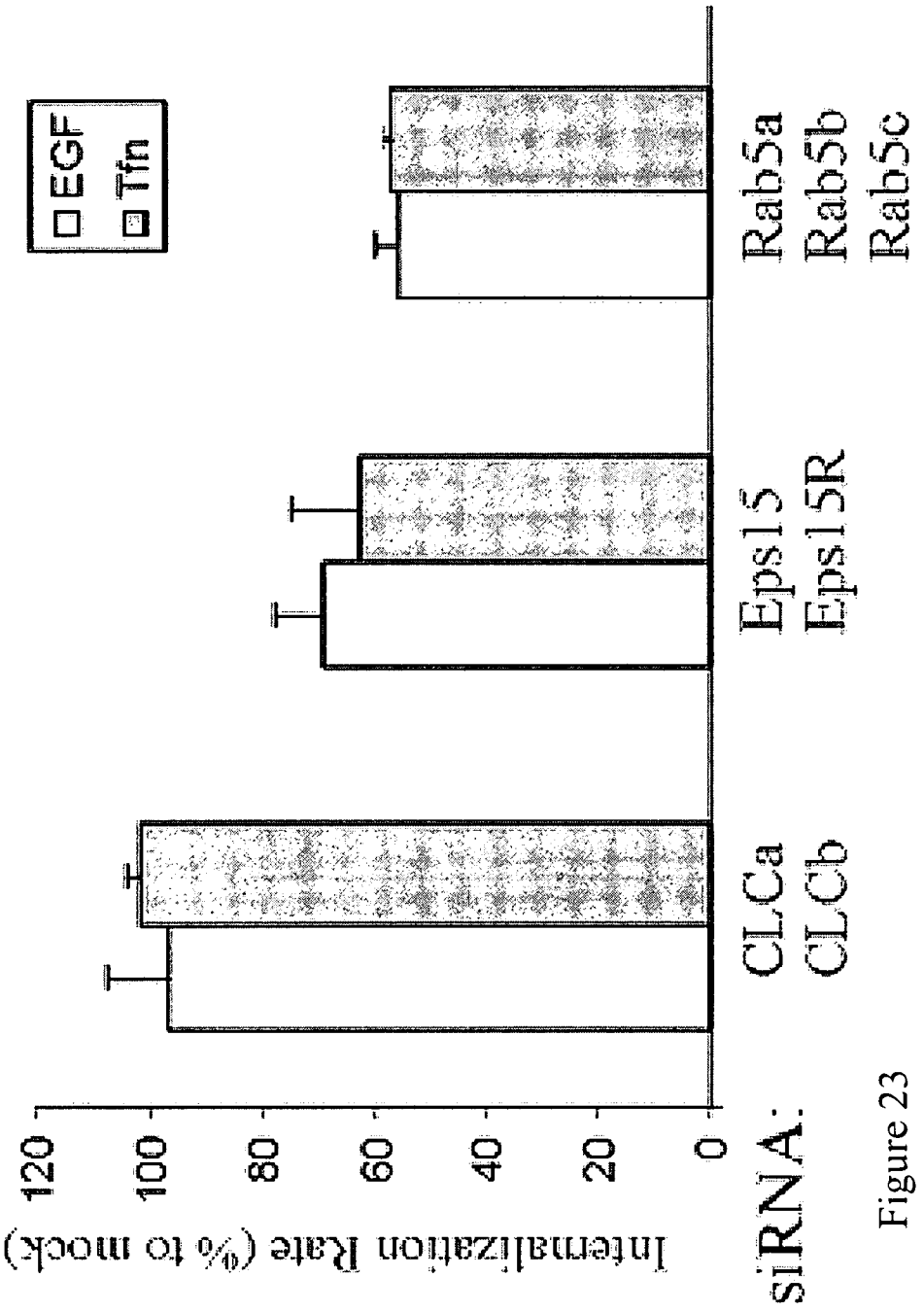

EGF
Tfn
Internalization Rate (% to mock)
120
100
80
60
40
20
0
siRNA:
CLCa
CLCb
Eps15
Eps15R
Rab5a
Rab5b
Rab5c

Figure 23

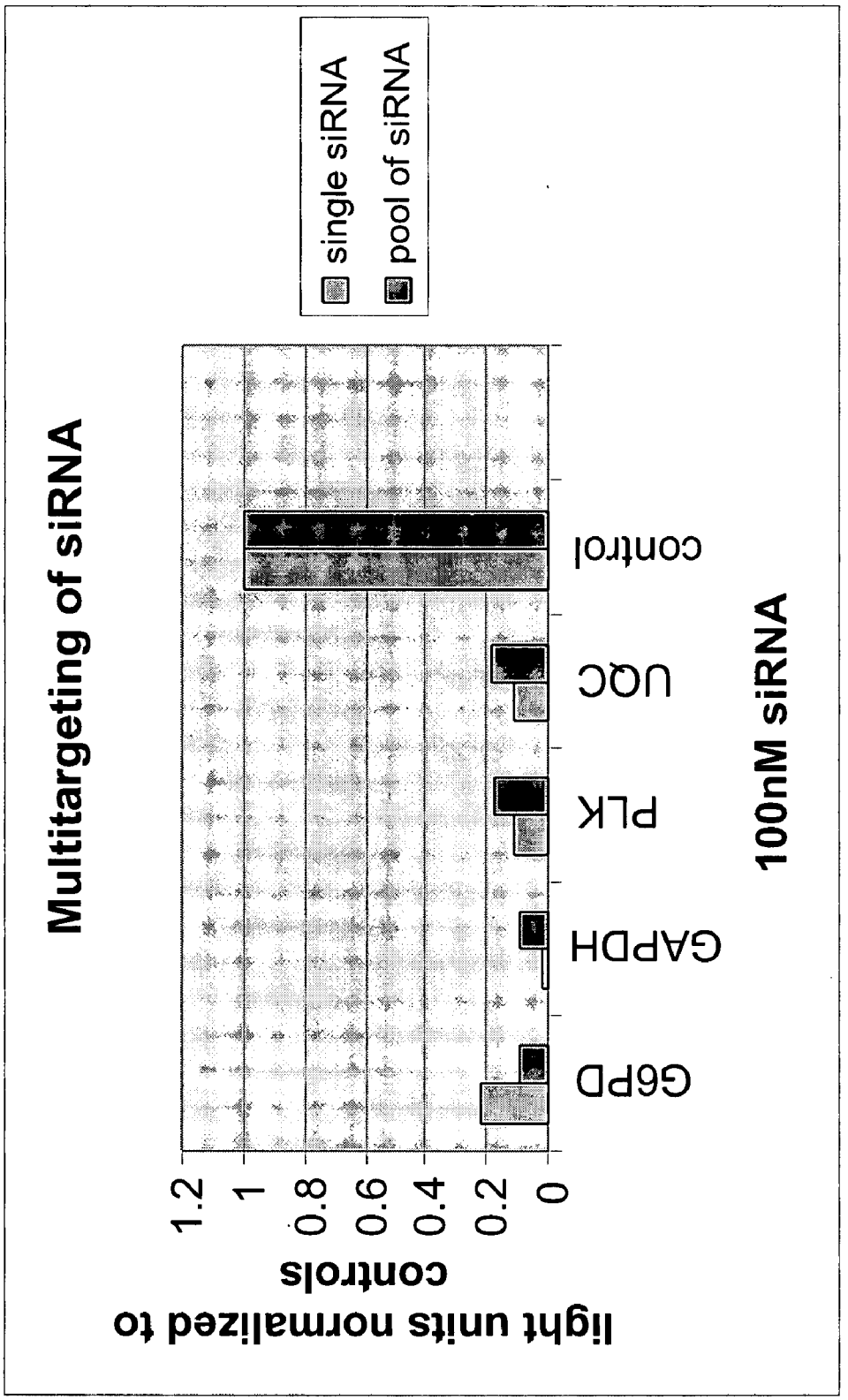
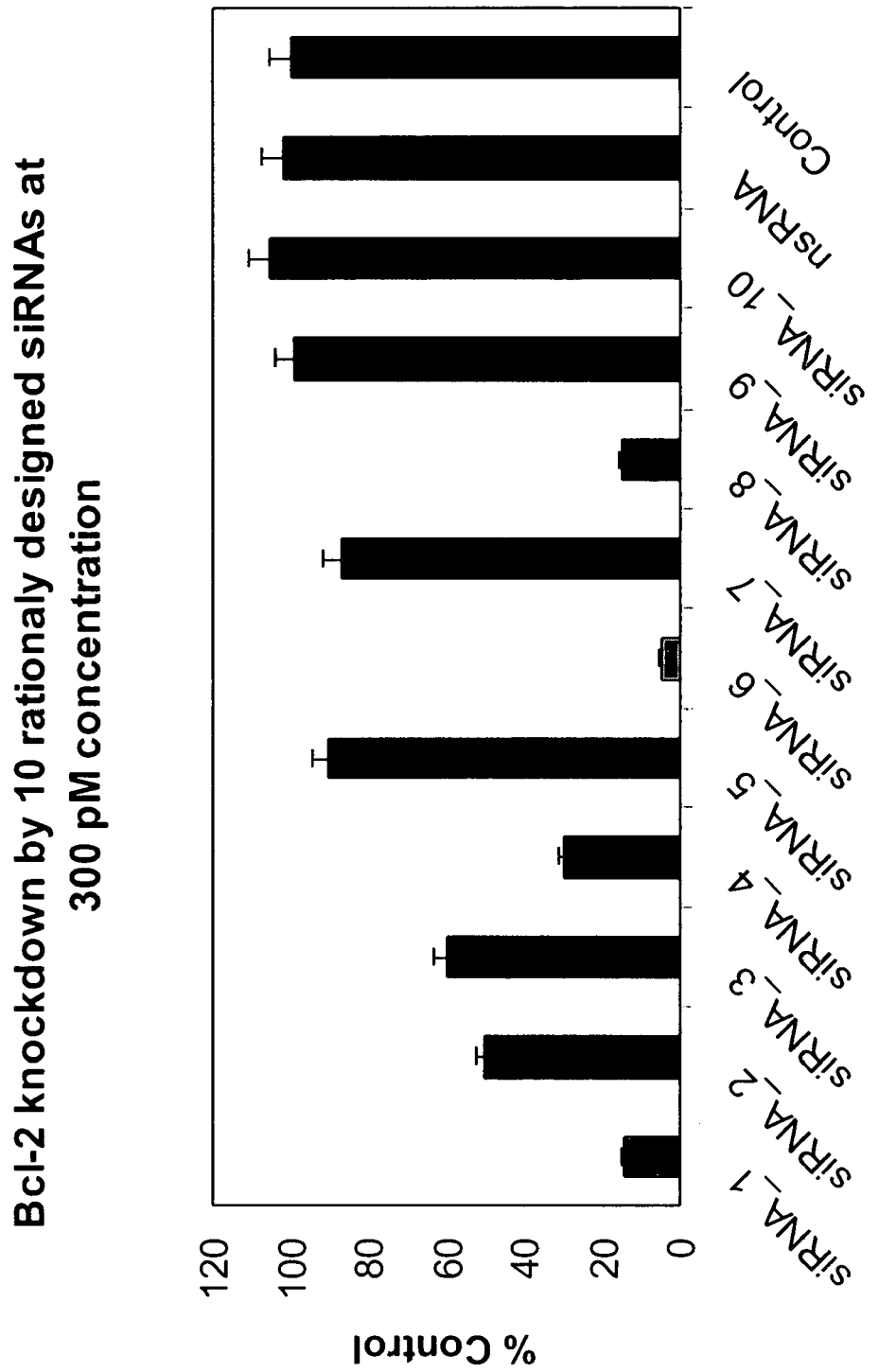

Multitargeting of siRNA
single siRNA
pool of siRNA
light units normalized to controls
1.2
1
0.8
0.6
0.4
0.2
0
G6PD
GAPDH
PLK
UQC
control
100nM siRNA

Figure 24

Figure 25


Bcl-2 knockdown by 10 rationaly designed siRNAs at 300 pM concentration
% Control
120
100
80
60
40
20
0
siRNA_1
siRNA_2
siRNA_3
siRNA_4
siRNA_5
siRNA_6
siRNA_7
siRNA_8
siRNA_9
siRNA_10
nsRNA
Control

SIRNA TARGETING PITUITARY TUMOR-TRANSFORMING 1 (PTTG1)

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation-in-part of U.S. Ser. No. 10/714,333, filed Nov. 14, 2003, which claims the benefit of U.S. Provisional Application No. 60/426,137, filed Nov. 14, 2002, and also claims the benefit of U.S. Provisional Application No. 60/502,050, filed Sep. 10, 2003; this application is also a continuation-in-part of U.S. Ser. No. 10/940,892, filed Sep. 14, 2004, which is a continuation of PCT Application No. PCT/US 04/14885, international filing date May 12, 2004. The disclosures of the priority applications, including the sequence listings and tables submitted in electronic form in lieu of paper, are incorporated by reference into the instant specification.

SEQUENCE LISTING

[0002] The sequence listing for this application has been submitted in accordance with 37 CFR § 1.52(e) and 37 CFR § 1.821 on CD-ROM in lieu of paper on a disk containing the sequence listing file entitled "DHARMA_2100-US45_CRF.txt" created May 30, 2007, 88 kb. Applicants hereby incorporate by reference the sequence listing provided on CD-ROM in lieu of paper into the instant specification.

FIELD OF INVENTION

[0003] The present invention relates to RNA interference ("RNAi").

BACKGROUND OF THE INVENTION

[0004] Relatively recently, researchers observed that double stranded RNA ("dsRNA") could be used to inhibit protein expression. This ability to silence a gene has broad potential for treating human diseases, and many researchers and commercial entities are currently investing considerable resources in developing therapies based on this technology.

[0005] Double stranded RNA induced gene silencing can occur on at least three different levels: (i) transcription inactivation, which refers to RNA guided DNA or histone methylation; (ii) siRNA induced mRNA degradation; and (iii) mRNA induced transcriptional attenuation.

[0006] It is generally considered that the major mechanism of RNA induced silencing (RNA interference, or RNAi) in mammalian cells is mRNA degradation. Initial attempts to use RNAi in mammalian cells focused on the use of long strands of dsRNA. However, these attempts to induce RNAi met with limited success, due in part to the induction of the interferon response, which results in a general, as opposed to a target-specific, inhibition of protein synthesis. Thus, long dsRNA is not a viable option for RNAi in mammalian systems.

[0007] More recently it has been shown that when short (18-30 bp) RNA duplexes are introduced into mammalian cells in culture, sequence-specific inhibition of target mRNA can be realized without inducing an interferon response. Certain of these short dsRNAs, referred to as small inhibitory RNAs ("siRNAs"), can act catalytically at sub-molar concentrations to cleave greater than 95% of the target mRNA in the cell. A description of the mechanisms for siRNA activity, as well as some of its applications are described in Provost et al. (2002) Ribonuclease Activity and RNA Binding of Recombinant Human Dicer, *EMBO J.* 21(21): 5864-5874; Tabara et al. (2002) The dsRNA Binding Protein RDE-4 Interacts with RDE-1, DCR-1 and a DexH-box Helicase to Direct RNAi in *C. elegans, Cell* 109(7):861-71; Ketting et al. (2002) Dicer Functions in RNA Interference and in Synthesis of Small RNA Involved in Developmental Timing in *C. elegans*; Martinez et al., Single-Stranded Antisense siRNAs Guide Target RNA Cleavage in RNAi, *Cell* 110(5):563; Hutvagner & Zamore (2002) A microRNA in a multiple-turnover RNAi enzyme complex, *Science* 297:2056.

[0008] From a mechanistic perspective, introduction of long double stranded RNA into plants and invertebrate cells is broken down into siRNA by a Type III endonuclease known as Dicer. Sharp, *RNA interference*—2001, Genes Dev. 2001, 15:485. Dicer, a ribonuclease-III-like enzyme, processes the dsRNA into 19-23 base pair short interfering RNAs with characteristic two base 3' overhangs. Bernstein, Caudy, Hammond, & Hannon (2001) Role for a bidentate ribonuclease in the initiation step of RNA interference, *Nature* 409:363. The siRNAs are then incorporated into an RNA-induced silencing complex (RISC) where one or more helicases unwind the siRNA duplex, enabling the complementary antisense strand to guide target recognition. Nykanen, Haley, & Zamore (2001) ATP requirements and small interfering RNA structure in the RNA interference pathway, *Cell* 107:309. Upon binding to the appropriate target mRNA, one or more endonucleases within the RISC cleaves the target to induce silencing. Elbashir, Lendeckel, & Tuschl (2001) RNA interference is mediated by 21- and 22-nucleotide RNAs, *Genes Dev.* 15:188, FIG. 1.

[0009] The interference effect can be long lasting and may be detectable after many cell divisions. Moreover, RNAi exhibits sequence specificity. Kisielow, M. et al. (2002) Isoform-specific knockdown and expression of adaptor protein ShcA using small interfering RNA, *J. Biochem.* 363:1-5. Thus, the RNAi machinery can specifically knock down one type of transcript, while not affecting closely related mRNA. These properties make siRNA a potentially valuable tool for inhibiting gene expression and studying gene function and drug target validation. Moreover, siRNAs are potentially useful as therapeutic agents against: (1) diseases that are caused by over-expression or misexpression of genes; and (2) diseases brought about by expression of genes that contain mutations.

[0010] Successful siRNA-dependent gene silencing depends on a number of factors. One of the most contentious issues in RNAi is the question of the necessity of siRNA design, i.e., considering the sequence of the siRNA used. Early work in *C. elegans* and plants circumvented the issue of design by introducing long dsRNA (see, for instance, Fire, A. et al. (1998) *Nature* 391:806-811). In this primitive organism, long dsRNA molecules are cleaved into siRNA by Dicer, thus generating a diverse population of duplexes that can potentially cover the entire transcript. While some fraction of these molecules are non-functional (i.e., induce little or no silencing) one or more have the potential to be highly functional, thereby silencing the gene of interest and alleviating the need for siRNA design. Unfortunately, due to the interferon response, this same approach is unavailable

for mammalian systems. While this effect can be circumvented by bypassing the Dicer cleavage step and directly introducing siRNA, this tactic carries with it the risk that the chosen siRNA sequence may be non-functional or semi-functional.

[0011] A number of researches have expressed the view that siRNA design is not a crucial element of RNAi. On the other hand, others in the field have begun to explore the possibility that RNAi can be made more efficient by paying attention to the design of the siRNA. Unfortunately, none of the reported methods have provided a satisfactory scheme for reliably selecting siRNA with acceptable levels of functionality. Accordingly, there is a need to develop rational criteria by which to select siRNA with an acceptable level of functionality, and to identify siRNA that have this improved level of functionality, as well as to identify siRNAs that are hyperfunctional.

SUMMARY OF THE INVENTION

[0012] The present invention is directed to increasing the efficiency of RNAi, particularly in mammalian systems. Accordingly, the present invention provides kits, siRNAs and methods for increasing siRNA efficacy.

[0013] According to a first embodiment, the present invention provides a kit for gene silencing, wherein said kit is comprised of a pool of at least two siRNA duplexes, each of which is comprised of a sequence that is complementary to a portion of the sequence of one or more target messenger RNA, and each of which is selected using non-target specific criteria.

[0014] According to a second embodiment, the present invention provides a method for selecting an siRNA, said method comprising applying selection criteria to a set of potential siRNA that comprise 18-30 base pairs, wherein said selection criteria are non-target specific criteria, and said set comprises at least two siRNAs and each of said at least two siRNAs contains a sequence that is at least substantially complementary to a target gene; and determining the relative functionality of the at least two siRNAs.

[0015] According to a third embodiment, the present invention also provides a method for selecting an siRNA wherein said selection criteria are embodied in a formula comprising:

$$(-14)*G_{13}-13*A_1-12*U_7-11*U_2-10*A_{11}-10*U_4-10*C_3-10*C_5-10*C_6-9*A_{10}-9*U_9-9*C_{18}-8*G_{10}-7*U_1-7*U_{16}-7*C_{17}-7*C_{19}+7*U_{17}+8*A_2+8*A_4+8*A_5+8*C_4+9*G_8+10*A_7+10*U_{18}+11*A_{19}+11*C_9+15*G_1+18*A_3+19*U_{10}-Tm-3*(GC_{total})-6*(GC_{15-19})-30*X; \text{ or} \quad \text{Formula VIII:}$$

$$(-8)*A1+(-1)*A2+(12)*A3+(7)*A4+(18)*A5+(12)*A6+(19)*A7+(6)*A8+(-4)*A9+(-5)*A10+(-2)*A11+(-5)*A12+(17)*A13+(-3)*A14+(4)*A15+(2)*A16+(8)*A17+(11)*A18+(30)*A19+(-13)*U1+(-10)*U2+(2)*U3+(-2)*U4+(-5)*U5+(5)*U6+(-2)*U7+(-10)*U8+(-5)*U9+(15)*U10+(-1)*U11+(0)*U12+(10)*U13+(-9)*U14+(-13)*U15+(-10)*U16+(3)*U17+(9)*U18+(9)*U19+(7)*C1+(3)*C2+(-21)*C3+(5)*C4+(-9)*C5+(-20)*C6+(-18)*C7+(-5)*C8+(5)*C9+(1)*C10+(2)*C11+(-5)*C12+(-3)*C13+(-6)*C14+(-2)*C15+(-5)*C16+(-3)*C17+(-12)*C18+(-18)*C19+(14)*G1+(8)*G2+(7)*G3+(-10)*G4+(-4)*G5+(2)*G6+(1)*G7+(9)*G8+(5)*G9+(-11)*G10+(1)*G11+(9)*G12+(-24)*G13+(18)*G14+(11)*G15+(13)*G16+(-7)*G17+(-9)*G18+(-22)*G19+6*(\text{number of A+U in position 15-19})-3*(\text{number of G+C in whole siRNA}), \quad \text{Formula X}$$

wherein position numbering begins at the 5'-most position of a sense strand, and

[0016] A_1=1 if A is the base at position 1 of the sense strand, otherwise its value is 0;

[0017] A_2=1 if A is the base at position 2 of the sense strand, otherwise its value is 0;

[0018] A_3=1 if A is the base at position 3 of the sense strand, otherwise its value is 0;

[0019] A_4=1 if A is the base at position 4 of the sense strand, otherwise its value is 0;

[0020] A_5=1 if A is the base at position 5 of the sense strand, otherwise its value is 0;

[0021] A_6=1 if A is the base at position 6 of the sense strand, otherwise its value is 0;

[0022] A_7=1 if A is the base at position 7 of the sense strand, otherwise its value is 0;

[0023] A_{10}=1 if A is the base at position 10 of the sense strand, otherwise its value is 0;

[0024] A_{11}=1 if A is the base at position 11 of the sense strand, otherwise its value is 0;

[0025] A_{13}=1 if A is the base at position 13 of the sense strand, otherwise its value is 0;

[0026] A_{19}=1 if A is the base at position 19 of the sense strand, otherwise if another base is present or the sense strand is only 18 base pairs in length, its value is 0;

[0027] C_3=1 if C is the base at position 3 of the sense strand, otherwise its value is 0;

[0028] C_4=1 if C is the base at position 4 of the sense strand, otherwise its value is 0;

[0029] C_5=1 if C is the base at position 5 of the sense strand, otherwise its value is 0;

[0030] C_6=1 if C is the base at position 6 of the sense strand, otherwise its value is 0;

[0031] C_7=1 if C is the base at position 7 of the sense strand, otherwise its value is 0;

[0032] C_9=1 if C is the base at position 9 of the sense strand, otherwise its value is 0;

[0033] C_{17}=1 if C is the base at position 17 of the sense strand, otherwise its value is 0;

[0034] C_{18}=1 if C is the base at position 18 of the sense strand, otherwise its value is 0;

[0035] C_{19}=1 if C is the base at position 19 of the sense strand, otherwise if another base is present or the sense strand is only 18 base pairs in length, its value is 0;

[0036] G_1=1 if G is the base at position 1 on the sense strand, otherwise its value is 0;

[0037] G_2=1 if G is the base at position 2 of the sense strand, otherwise its value is 0;

[0038] G_8=1 if G is the base at position 8 on the sense strand, otherwise its value is 0;

[0039] G_{10}=1 if G is the base at position 10 on the sense strand, otherwise its value is 0;

[0040] G_{13}=1 if G is the base at position 13 on the sense strand, otherwise its value is 0;

[0041] G_{19}=1 if G is the base at position 19 of the sense strand, otherwise if another base is present or the sense strand is only 18 base pairs in length, its value is 0;

[0042] U_1=1 if U is the base at position 1 on the sense strand, otherwise its value is 0;

[0043] U_2=1 if U is the base at position 2 on the sense strand, otherwise its value is 0;

[0044] U_3=1 if U is the base at position 3 on the sense strand, otherwise its value is 0;

[0045] U_4=1 if U is the base at position 4 on the sense strand, otherwise its value is 0;

[0046] U_7=1 if U is the base at position 7 on the sense strand, otherwise its value is 0;

[0047] U_9=1 if U is the base at position 9 on the sense strand, otherwise its value is 0;

[0048] U_{10}=1 if U is the base at position 10 on the sense strand, otherwise its value is 0;

[0049] U_{15}=1 if U is the base at position 15 on the sense strand, otherwise its value is 0;

[0050] U_{16}=1 if U is the base at position 16 on the sense strand, otherwise its value is 0;

[0051] U_{17}=1 if U is the base at position 17 on the sense strand, otherwise its value is 0;

[0052] U_{18}=1 if U is the base at position 18 on the sense strand, otherwise its value is 0.

[0053] $GC_{15\text{-}19}$=the number of G and C bases within positions 15-19 of the sense strand, or within positions 15-18 if the sense strand is only 18 base pairs in length;

[0054] GC_{total}=the number of G and C bases in the sense strand;

[0055] Tm=100 if the siRNA oligo has the internal repeat longer then 4 base pairs, otherwise its value is 0; and

[0056] X=the number of times that the same nucleotide repeats four or more times in a row.

[0057] According to a fourth embodiment, the invention provides a method for developing an algorithm for selecting siRNA, said method comprising: (a) selecting a set of siRNA; (b) measuring gene silencing ability of each siRNA from said set; (c) determining relative functionality of each siRNA; (d) determining improved functionality by the presence or absence of at least one variable selected from the group consisting of the presence or absence of a particular nucleotide at a particular position, the total number of As and Us in positions 15-19, the number of times that the same nucleotide repeats within a given sequence, and the total number of Gs and Cs; and (e) developing an algorithm using the information of step (d).

[0058] According to a fifth embodiment, the present invention provides a kit, wherein said kit is comprised of at least two siRNAs, wherein said at least two siRNAs comprise a first optimized siRNA and a second optimized siRNA, wherein said first optimized siRNA and said second optimized siRNA are optimized according a formula comprising Formula X.

[0059] The present invention also provides a method for identifying a hyperfunctional siRNA, comprising applying selection criteria to a set of potential siRNA that comprise 18-30 base pairs, wherein said selection criteria are non-target specific criteria, and said set comprises at least two siRNAs and each of said at least two siRNAs contains a sequence that is at least substantially complementary to a target gene; determining the relative functionality of the at least two siRNAs and assigning each of the at least two siRNAs a functionality score; and selecting siRNAs from the at least two siRNAs that have a functionality score that reflects greater than 80 percent silencing at a concentration in the picomolar range, wherein said greater than 80 percent silencing endures for greater than 120 hours.

[0060] According to a sixth embodiment, the present invention provides a hyperfunctional siRNA that is capable of silencing Bcl2.

[0061] According to a seventh embodiment, the present invention provides a method for developing an siRNA algorithm for selecting functional and hyperfunctional siRNAs for a given sequence. The method comprises:

[0062] (a) selecting a set of siRNAs;

[0063] (b) measuring the gene silencing ability of each siRNA from said set;

[0064] (c) determining the relative functionality of each siRNA;

[0065] (d) determining the amount of improved functionality by the presence or absence of at least one variable selected from the group consisting of the total GC content, melting temperature of the siRNA, GC content at positions 15-19, the presence or absence of a particular nucleotide at a particular position, relative thermodynamic stability at particular positions in a duplex, and the number of times that the same nucleotide repeats within a given sequence; and

[0066] (e) developing an algorithm using the information of step (d).

[0067] According to this embodiment, preferably the set of siRNAs comprises at least 90 siRNAs from at least one gene, more preferably at least 180 siRNAs from at least two different genes, and most preferably at least 270 and 360 siRNAs from at least three and four different genes, respectively. Additionally, in step (d) the determination is made with preferably at least two, more preferably at least three, even more preferably at least four, and most preferably all of the variables. The resulting algorithm is not target sequence specific.

[0068] In another embodiment, the present invention provides rationally designed siRNAs identified using the formulas above.

[0069] In yet another embodiment, the present invention is directed to hyperfunctional siRNA.

[0070] The ability to use the above algorithms, which are not sequence or species specific, allows for the cost-effective selection of optimized siRNAs for specific target sequences. Accordingly, there will be both greater efficiency and reliability in the use of siRNA technologies.

[0071] In various embodiments, siRNAs that target pituitary tumor-transforming 1 (PTTG1) are provided. In vari-

ous embodiments, the siRNAs are rationally designed. In various embodiments, the siRNAs are functional or hyperfunctional.

[0072] In various embodiments, an siRNA that targets PTTG1 is provided, wherein the siRNA is selected from the group consisting of various siRNA sequences targeting PTTG1 that are disclosed herein. In various embodiments, the siRNA sequence is selected from the group consisting of SEQ ID NO. 438 to SEQ ID NO. 498.

[0073] In various embodiments, siRNA comprising a sense region and an antisense region are provided, wherein said sense region and said antisense region are at least 90% complementary, said sense region and said antisense region together form a duplex region comprising 18-30 base pairs, and said sense region comprises a sequence that is at least 90% similar to a sequence selected from the group consisting of siRNA sequences targeting PTTG1 that are disclosed herein. In various embodiments, the siRNA sequence is selected from the group consisting of SEQ ID NO. 438 to SEQ ID NO. 498.

[0074] In various embodiments, an siRNA comprising a sense region and an antisense region is provided, wherein said sense region and said antisense region are at least 90% complementary, said sense region and said antisense region together form a duplex region comprising 18-30 base pairs, and said sense region comprises a sequence that is identical to a contiguous stretch of at least 18 bases of a sequence selected from the group consisting of SEQ ID NO. 438 to SEQ ID NO. 498. In various embodiments, the duplex region is 19-30 base pairs, and the sense region comprises a sequence that is identical to a sequence selected from the group consisting of SEQ ID NO. 438 to SEQ ID NO. 498.

[0075] In various embodiments, a pool of at least two siRNAs is provided, wherein said pool comprises a first siRNA and a second siRNA, said first siRNA comprising a duplex region of length 18-30 base pairs that has a first sense region that is at least 90% similar to 18 bases of a first sequence selected from the group consisting of SEQ ID NO. 438 to SEQ ID NO. 498, and said second siRNA comprises a duplex region of length 18-30 base pairs that has a second sense region that is at least 90% similar to 18 bases of a second sequence selected from the group consisting of SEQ ID NO. 438 to SEQ ID NO. 498, wherein said first sense region and said second sense region are not identical.

[0076] In various embodiments, the first sense region comprises a sequence that is identical to at least 18 bases of a sequence selected from the group consisting of SEQ ID NO. 438 to SEQ ID NO. 498, and said second sense region comprises a sequence that is identical to at least 18 bases of a sequence selected from the group consisting of SEQ ID NO. 438 to SEQ ID NO. 498. In various embodiments, the duplex of said first siRNA is 19-30 base pairs, and said first sense region comprises a sequence that is at least 90% similar to a sequence selected from the group consisting of SEQ ID NO. 438 to SEQ ID NO. 498, and said duplex of said second siRNA is 19-30 base pairs and comprises a sequence that is at least 90% similar to a sequence selected from the group consisting of SEQ ID NO. 438 to SEQ ID NO. 498.

[0077] In various embodiments, the duplex of said first siRNA is 19-30 base pairs and said first sense region comprises a sequence that is identical to at least 18 bases of a sequence selected from the group consisting of SEQ ID NO. 438 to SEQ ID NO. 498, and said duplex of said second siRNA is 19-30 base pairs and said second region comprises a sequence that is identical to a sequence selected from the group consisting of SEQ ID NO. 438 to SEQ ID NO. 498.

[0078] For a better understanding of the present invention together with other and further advantages and embodiments, reference is made to the following description taken in conjunction with the examples, the scope of which is set forth in the appended claims.

BRIEF DESCRIPTION OF THE FIGURES

[0079] FIG. **1** shows a model for siRNA-RISC interactions. RISC has the ability to interact with either end of the siRNA or miRNA molecule. Following binding, the duplex is unwound, and the relevant target is identified, cleaved, and released.

[0080] FIG. **2** is a representation of the functionality of two hundred and seventy siRNA duplexes that were generated to target human cyclophilin, human diazepam-binding inhibitor (DB), and firefly luciferase.

[0081] FIG. **3***a* is a representation of the silencing effect of 30 siRNAs in three different cells lines, HEK293, DU145, and Hela. FIG. **3***b* shows the frequency of different functional groups (>95% silencing (black), >80% silencing (gray), >50% silencing (dark gray), and <50% silencing (white)) based on GC content. In cases where a given bar is absent from a particular GC percentage, no siRNA were identified for that particular group. FIG. **3***c* shows the frequency of different functional groups based on melting temperature (Tm).

[0082] FIGS. **4**A-**4**E are representations of a statistical analysis that revealed correlations between silencing and five sequence-related properties of siRNA: (A) an A at position 19 of the sense strand, (B) an A at position 3 of the sense strand, (C) a U at position 10 of the sense strand, (D) a base other than G at position 13 of the sense strand, and (E) a base other than C at position 19 of the sense strand. All variables were correlated with siRNA silencing of firefly luciferase and human cyclophilin. siRNAs satisfying the criterion are grouped on the left (Selected) while those that do not, are grouped on the right (Eliminated). Y-axis is "% Silencing of Control." Each position on the X-axis represents a unique siRNA.

[0083] FIGS. **5**A and **5**B are representations of firefly luciferase and cyclophilin siRNA panels sorted according to functionality and predicted values using Formula VIII. The siRNA found within the circle represent those that have Formula VIII values (SMARTSCORES™, or siRNA rank) above zero. siRNA outside the indicated area have calculated Formula VIII values that are below zero. Y-axis is "Expression (% Control)." Each position on the X-axis represents a unique siRNA.

[0084] FIG. **6**A is a representation of the average internal stability profile (AISP) derived from 270 siRNAs taken from three separate genes (cyclophilin B, DBI and firefly luciferase). Graphs represent AISP values of highly functional, functional, and non-functional siRNA. FIG. **6**B is a comparison between the AISP of naturally derived GFP siRNA (filled squares) and the AISP of siRNA from cyclo-

philin B, DBI, and luciferase having >90% silencing properties (no fill) for the antisense strand. "DG" is the symbol for ΔG, free energy.

[0085] FIG. **7** is a histogram showing the differences in duplex functionality upon introduction of base pair mismatches. The X-axis shows the mismatch introduced in the siRNA and the position it is introduced (e.g., 8C>A reveals that position 8 (which normally has a C) has been changed to an A). The Y-axis is "% Silencing (Normalized to Control)." The samples on the X-axis represent siRNAs at 100 nM and are, reading from left to right: 1A to C, 1A to G, 1A to U; 2A to C, 2A to G, 2A to U; 3A to C, 3A to G, 3A to U; 4G to A, 4G to C; 4G to U; 5U to A, 5U to C, 5U to G; 6U to A, 6U to C, 6U to G; 7G to A, 7G to C, 7G to U; 8C to A, 8C to G, 8C to U; 9G to A, 9G to C, 9G to U; 10C to A, 10C to G, 10C to U; 11G to A, 11G to C, 11G to U; 12G to A, 12G to C, 12G to U; 13A to C, 13A to G, 13A to U; 14G to A, 14G to C, 14G to U; 15G to A, 15G to C, 15G to U; 16A to C, 16A to G, 16A to U; 17G to A, 17G to C, 17G to U; 18U to A, 18U to C, 18U to G; 19U to A, 19U to C, 19U to G; 20 wt; Control.

[0086] FIG. **8**A is histogram that shows the effects of 5'sense and antisense strand modification with 2'-O-methylation on functionality. FIG. **8**B is an expression profile showing a comparison of sense strand off-target effects for IGF1R-3 and 2'-O-methyl IGF1R-3. Sense strand off-targets (lower box) are not induced when the 5' end of the sense strand is modified with 2'-O-methyl groups (top box).

[0087] FIG. **9** shows a graph of SMARTSCORES™, or siRNA rank, versus RNAi silencing values for more than 360 siRNA directed against 30 different genes. SiRNA to the right of the vertical bar represent those siRNA that have desirable SMARTSCORES™, or siRNA rank.

[0088] FIGS. **10**A-E compare the RNAi of five different genes (SEAP, DBI, PLK, Firefly Luciferase, and *Renilla* Luciferase) by varying numbers of randomly selected siRNA and four rationally designed (SMART-selected) siRNA chosen using the algorithm described in Formula VIII. In addition, RNAi induced by a pool of the four SMART-selected siRNA is reported at two different concentrations (100 and 400 nM). **10**F is a comparison between a pool of randomly selected EGFR siRNA (Pool 1) and a pool of SMART-selected EGFR siRNA (Pool 2). Pool 1, S1-S4 and Pool 2 S1-S4 represent the individual members that made up each respective pool. Note that numbers for random siRNAs represent the position of the 5' end of the sense strand of the duplex. The Y-axis represents the % expression of the control(s). The X-axis is the percent expression of the control.

[0089] FIG. **11** shows the Western blot results from cells treated with siRNA directed against twelve different genes involved in the clathrin-dependent endocytosis pathway (CHC, DynII, CALM, CLCa, CLCb, Eps15, Eps15R, Rab5a, Rab5b, Rab5c, β2 subunit of AP-2 and EEA.1). siRNA were selected using Formula VIII. "Pool" represents a mixture of duplexes 1-4. Total concentration of each siRNA in the pool is 25 nM. Total concentration=4×25=100 nM.

[0090] FIG. **12** is a representation of the gene silencing capabilities of rationally-selected siRNA directed against ten different genes (human and mouse cyclophilin, C-myc, human lamin A/C, QB (ubiquinol-cytochrome c reductase core protein I), MEK1 and MEK2, ATE1 (arginyl-tRNA protein transferase), GAPDH, and Eg5). The Y-axis is the percent expression of the control. Numbers 1, 2, 3 and 4 represent individual rationally selected siRNA. "Pool" represents a mixture of the four individual siRNA.

[0091] FIG. **13** is the sequence of the top ten Bcl2 siRNAs as determined by Formula VIII. Sequences are listed 5' to 3'.

[0092] FIG. **14** is the knockdown by the top ten Bcl2 siRNAs at 100 nM concentrations. The Y-axis represents the amount of expression relative to the non-specific (ns) and transfection mixture control.

[0093] FIG. **15** represents a functional walk where siRNA beginning on every other base pair of a region of the luciferase gene are tested for the ability to silence the luciferase gene. The Y-axis represents the percent expression relative to a control. The X-axis represents the position of each individual siRNA. Reading from left to right across the X-axis, the position designations are 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, and Plasmid.

[0094] FIGS. **16**A and **16**B are histograms demonstrating the inhibition of target gene expression by pools of 2 (**16**A) and 3 (**16**B) siRNA duplexes taken from the walk described in FIG. **15**. The Y-axis in each represents the percent expression relative to control. The X-axis in each represents the position of the first siRNA in paired pools, or trios of siRNAs. For instance, the first paired pool contains siRNAs 1 and 3. The second paired pool contains siRNAs 3 and 5. Pool 3 (of paired pools) contains siRNAs 5 and 7, and so on. For each of **16**A and **16**B, the X-axis from left to right reads 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, and Plasmid.

[0095] FIGS. **17**A and **17**B are histograms demonstrating the inhibition of target gene expression by pools of 4 (**17**A) and 5 (**17**B) siRNA duplexes. The Y-axis in each represents the percent expression relative to control. The X-axis in each represents the position of the first siRNA in each pool. For each of **17**A and **17**B, the X-axis from left to right reads 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, and Plasmid.

[0096] FIGS. **18**A and **18**B are histograms demonstrating the inhibition of target gene expression by siRNAs that are ten (**18**A) and twenty (**18**B) base pairs base pairs apart. The Y-axis represents the percent expression relative to a control. The X-axis represents the position of the first siRNA in each pool. For each of **18**A and **18**B, the X-axis from left to right reads 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, and Plasmid.

[0097] FIG. **19** shows that pools of siRNAs (dark gray bar) work as well (or better) than the best siRNA in the pool (light gray bar). The Y-axis represents the percent expression relative to a control. The X-axis represents the position of the first siRNA in each pool. The X-axis from left to right reads 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, and Plasmid.

[0098] FIG. **20** shows that the combination of several semifunctional siRNAs (dark gray) result in a significant improvement of gene expression inhibition over individual (semi-functional; light gray) siRNA. The Y-axis represents the percent expression relative to a control.

[0099] FIGS. **21**A, **21**B and **21**C show both pools (Library, Lib) and individual siRNAs in inhibition of gene expression of Beta-Galactosidase, *Renilla* Luciferase and SEAP (alkaline phosphatase). Numbers on the X-axis indicate the position of the 5'-most nucleotide of the sense strand of the duplex. The Y-axis represents the percent expression of each gene relative to a control. Libraries contain 19 nucleotide long siRNAs (not including overhangs) that begin at the following nucleotides: SEAP: Lib 1: 206, 766, 812, 923, Lib 2: 1117, 1280, 1300, 1487, Lib 3: 206, 766, 812, 923, 1117, 1280, 1300, 1487, Lib 4: 206, 812, 1117, 1300, Lib 5: 766, 923, 1280, 1487, Lib 6: 206, 1487; Bgal: Lib 1: 979, 1339, 2029, 2590, Lib 2: 1087, 1783, 2399, 3257, Lib 3: 979, 1783, 2590, 3257, Lib 4: 979, 1087, 1339, 1783, 2029, 2399, 2590, 3257, Lib 5: 979, 1087, 1339, 1783, Lib 6: 2029, 2399, 2590, 3257; *Renilla*: Lib 1: 174, 300, 432, 568, Lib 2: 592, 633, 729, 867, Lib 3: 174, 300, 432, 568, 592, 633, 729, 867, Lib 4: 174, 432, 592, 729, Lib 5: 300, 568, 633, 867, Lib 6: 592, 568.

[0100] FIG. **22** shows the results of an EGFR and TfnR internalization assay when single gene knockdowns are performed. The Y-axis represents percent internalization relative to control.

[0101] FIG. **23** shows the results of an EGFR and TfnR internalization assay when multiple genes are knocked down (e.g., Rab5a, b, c). The Y-axis represents the percent internalization relative to control.

[0102] FIG. **24** shows the simultaneous knockdown of four different genes. siRNAs directed against G6PD, GAPDH, PLK, and UQC were simultaneously introduced into cells. Twenty-four hours later, cultures were harvested and assayed for mRNA target levels for each of the four genes. A comparison is made between cells transfected with individual siRNAs vs. a pool of siRNAs directed against all four genes.

[0103] FIG. **25** shows the functionality of ten siRNAs at 0.3 nM concentrations.

DETAILED DESCRIPTION

Definitions

[0104] Unless stated otherwise, the following terms and phrases have the meanings provided below:

Complementary

[0105] The term "complementary" refers to the ability of polynucleotides to form base pairs with one another. Base pairs are typically formed by hydrogen bonds between nucleotide units in antiparallel polynucleotide strands. Complementary polynucleotide strands can base pair in the Watson-Crick manner (e.g., A to T, A to U, C to G), or in any other manner that allows for the formation of duplexes. As persons skilled in the art are aware, when using RNA as opposed to DNA, uracil rather than thymine is the base that is considered to be complementary to adenosine. However, when a U is denoted in the context of the present invention, the ability to substitute a T is implied, unless otherwise stated.

[0106] Perfect complementarity or 100% complementarity refers to the situation in which each nucleotide unit of one polynucleotide strand can hydrogen bond with a nucleotide unit of a second polynucleotide strand. Less than perfect complementarity refers to the situation in which some, but not all, nucleotide units of two strands can hydrogen bond with each other. For example, for two 20-mers, if only two base pairs on each strand can hydrogen bond with each other, the polynucleotide strands exhibit 10% complementarity. In the same example, if 18 base pairs on each strand can hydrogen bond with each other, the polynucleotide strands exhibit 90% complementarity.

Deoxynucleotide

[0107] The term "deoxynucleotide" refers to a nucleotide or polynucleotide lacking a hydroxyl group (OH group) at the 2' and/or 3' position of a sugar moiety. Instead, it has a hydrogen bonded to the 2' and/or 3' carbon. Within an RNA molecule that comprises one or more deoxynucleotides, "deoxynucleotide" refers to the lack of an OH group at the 2' position of the sugar moiety, having instead a hydrogen bonded directly to the 2' carbon.

Deoxyribonucleotide

[0108] The terms "deoxyribonucleotide" and "DNA" refer to a nucleotide or polynucleotide comprising at least one sugar moiety that has an H, rather than an OH, at its 2' and/or 3'position.

Duplex Region

[0109] The phrase "duplex region" refers to the region in two complementary or substantially complementary polynucleotides that form base pairs with one another, either by Watson-Crick base pairing or any other manner that allows for a stabilized duplex between polynucleotide strands that are complementary or substantially complementary. For example, a polynucleotide strand having 21 nucleotide units can base pair with another polynucleotide of 21 nucleotide units, yet only 19 bases on each strand are complementary or substantially complementary, such that the "duplex region" has 19 base pairs. The remaining bases may, for example, exist as 5' and 3' overhangs. Further, within the duplex region, 100% complementarity is not required; substantial complementarity is allowable within a duplex region. Substantial complementarity refers to 79% or greater complementarity. For example, a mismatch in a duplex region consisting of 19 base pairs results in 94.7% complementarity, rendering the duplex region substantially complementary.

Filters

[0110] The term "filter" refers to one or more procedures that are performed on sequences that are identified by the algorithm. In some instances, filtering includes in silico procedures where sequences identified by the algorithm can be screened to identify duplexes carrying desirable or undesirable motifs. Sequences carrying such motifs can be selected for, or selected against, to obtain a final set with the preferred properties. In other instances, filtering includes wet lab experiments. For instance, sequences identified by one or more versions of the algorithm can be screened using any one of a number of procedures to identify duplexes that have hyperfunctional traits (e.g., they exhibit a high degree

of silencing at subnanomolar concentrations and/or exhibit high degrees of silencing longevity).

Gene Silencing

[0111] The phrase "gene silencing" refers to a process by which the expression of a specific gene product is lessened or attenuated. Gene silencing can take place by a variety of pathways. Unless specified otherwise, as used herein, gene silencing refers to decreases in gene product expression that results from RNA interference (RNAi), a defined, though partially characterized pathway whereby small inhibitory RNA (siRNA) act in concert with host proteins (e.g., the RNA induced silencing complex, RISC) to degrade messenger RNA (mRNA) in a sequence-dependent fashion. The level of gene silencing can be measured by a variety of means, including, but not limited to, measurement of transcript levels by Northern Blot Analysis, B-DNA techniques, transcription-sensitive reporter constructs, expression profiling (e.g., DNA chips), and related technologies. Alternatively, the level of silencing can be measured by assessing the level of the protein encoded by a specific gene. This can be accomplished by performing a number of studies including Western Analysis, measuring the levels of expression of a reporter protein that has e.g., fluorescent properties (e.g., GFP) or enzymatic activity (e.g., alkaline phosphatases), or several other procedures.

miRNA

[0112] The term "miRNA" refers to microRNA.

Nucleotide

[0113] The term "nucleotide" refers to a ribonucleotide or a deoxyribonucleotide or modified form thereof, as well as an analog thereof. Nucleotides include species that comprise purines, e.g., adenine, hypoxanthine, guanine, and their derivatives and analogs, as well as pyrimidines, e.g., cytosine, uracil, thymine, and their derivatives and analogs.

[0114] Nucleotide analogs include nucleotides having modifications in the chemical structure of the base, sugar and/or phosphate, including, but not limited to, 5-position pyrimidine modifications, 8-position purine modifications, modifications at cytosine exocyclic amines, and substitution of 5-bromo-uracil; and 2'-position sugar modifications, including but not limited to, sugar-modified ribonucleotides in which the 2'-OH is replaced by a group such as an H, OR, R, halo, SH, SR, NH_2, NHR, NR_2, or CN, wherein R is an alkyl moiety. Nucleotide analogs are also meant to include nucleotides with bases such as inosine, queuosine, xanthine, sugars such as 2'-methyl ribose, non-natural phosphodiester linkages such as methylphosphonates, phosphorothioates and peptides.

[0115] Modified bases refer to nucleotide bases such as, for example, adenine, guanine, cytosine, thymine, uracil, xanthine, inosine, and queuosine that have been modified by the replacement or addition of one or more atoms or groups. Some examples of types of modifications that can comprise nucleotides that are modified with respect to the base moieties include but are not limited to, alkylated, halogenated, thiolated, aminated, amidated, or acetylated bases, individually or in combination. More specific examples include, for example, 5-propynyluridine, 5-propynylcytidine, 6-methyladenine, 6-methylguanine, N,N,-dimethyladenine, 2-propyladenine, 2-propylguanine, 2-aminoadenine, 1-methylinosine, 3-methyluridine, 5-methylcytidine, 5-methyluridine and other nucleotides having a modification at the 5 position, 5-(2-amino)propyl uridine, 5-halocytidine, 5-halouridine, 4-acetylcytidine, 1-methyladenosine, 2-methyladenosine, 3-methylcytidine, 6-methyluridine, 2-methylguanosine, 7-methylguanosine, 2,2-dimethylguanosine, 5-methylaminoethyluridine, 5-methyloxyuridine, deazanucleotides such as 7-deaza-adenosine, 6-azouridine, 6-azocytidine, 6-azothymidine, 5-methyl-2-thiouridine, other thio bases such as 2-thiouridine and 4-thiouridine and 2-thiocytidine, dihydrouridine, pseudouridine, queuosine, archaeosine, naphthyl and substituted naphthyl groups, any O- and N-alkylated purines and pyrimidines such as N6-methyladenosine, 5-methylcarbonylmethyluridine, uridine 5-oxyacetic acid, pyridine-4-one, pyridine-2-one, phenyl and modified phenyl groups such as aminophenol or 2,4,6-trimethoxy benzene, modified cytosines that act as G-clamp nucleotides, 8-substituted adenines and guanines, 5-substituted uracils and thymines, azapyrimidines, carboxyhydroxyalkyl nucleotides, carboxyalkylaminoalkyl nucleotides, and alkylcarbonylalkylated nucleotides. Modified nucleotides also include those nucleotides that are modified with respect to the sugar moiety, as well as nucleotides having sugars or analogs thereof that are not ribosyl. For example, the sugar moieties may be, or be based on, mannoses, arabinoses, glucopyranoses, galactopyranoses, 4'-thioribose, and other sugars, heterocycles, or carbocycles.

[0116] The term nucleotide is also meant to include what are known in the art as universal bases. By way of example, universal bases include but are not limited to 3-nitropyrrole, 5-nitroindole, or nebularine. The term "nucleotide" is also meant to include the N3' to P5' phosphoramidate, resulting from the substitution of a ribosyl 3' oxygen with an amine group.

[0117] Further, the term nucleotide also includes those species that have a detectable label, such as for example a radioactive or fluorescent moiety, or mass label attached to the nucleotide.

Off-Target Silencing and Off-Target Interference

[0118] The phrases "off-target silencing" and "off-target interference" are defined as degradation of mRNA other than the intended target mRNA due to overlapping and/or partial homology with secondary mRNA messages.

Polynucleotide

[0119] The term "polynucleotide" refers to polymers of nucleotides, and includes but is not limited to DNA, RNA, DNA/RNA hybrids including polynucleotide chains of regularly and/or irregularly alternating deoxyribosyl moieties and ribosyl moieties (i.e., wherein alternate nucleotide units have an —OH, then and —H, then an —OH, then an —H, and so on at the 2' position of a sugar moiety), and modifications of these kinds of polynucleotides, wherein the attachment of various entities or moieties to the nucleotide units at any position are included.

Polyribonucleotide

[0120] The term "polyribonucleotide" refers to a polynucleotide comprising two or more modified or unmodified ribonucleotides and/or their analogs. The term "polyribonucleotide" is used interchangeably with the term "oligoribonucleotide."

Ribonucleotide and Ribonucleic Acid

[0121] The term "ribonucleotide" and the phrase "ribonucleic acid" (RNA), refer to a modified or unmodified nucleotide or polynucleotide comprising at least one ribonucleotide unit. A ribonucleotide unit comprises an hydroxyl group attached to the 2' position of a ribosyl moiety that has a nitrogenous base attached in N-glycosidic linkage at the 1' position of a ribosyl moiety, and a moiety that either allows for linkage to another nucleotide or precludes linkage.

siRNA

[0122] The term "siRNA" refers to small inhibitory RNA duplexes that induce the RNA interference (RNAi) pathway. These molecules can vary in length (generally 18-30 base pairs) and contain varying degrees of complementarity to their target mRNA in the antisense strand. Some, but not all, siRNA have unpaired overhanging bases on the 5' or 3' end of the sense strand and/or the antisense strand. The term "siRNA" includes duplexes of two separate strands, as well as single strands that can form hairpin structures comprising a duplex region.

[0123] siRNA may be divided into five (5) groups (non-functional, semi-functional, functional, highly functional, and hyper-functional) based on the level or degree of silencing that they induce in cultured cell lines. As used herein, these definitions are based on a set of conditions where the siRNA is transfected into said cell line at a concentration of 100 nM and the level of silencing is tested at a time of roughly 24 hours after transfection, and not exceeding 72 hours after transfection. In this context, "non-functional siRNA" are defined as those siRNA that induce less than 50% (<50%) target silencing. "Semi-functional siRNA" induce 50-79% target silencing. "Functional siRNA" are molecules that induce 80-95% gene silencing. "Highly-functional siRNA" are molecules that induce greater than 95% gene silencing. "Hyperfunctional siRNA" are a special class of molecules. For purposes of this document, hyper-functional siRNA are defined as those molecules that: (1) induce greater than 95% silencing of a specific target when they are transfected at subnanomolar concentrations (i.e., less than one nanomolar); and/or (2) induce functional (or better) levels of silencing for greater than 96 hours. These relative functionalities (though not intended to be absolutes) may be used to compare siRNAs to a particular target for applications such as functional genomics, target identification and therapeutics.

SMARTSCORE™, or siRNA Rank

[0124] The term "SMARTSCORE™", or "siRNA rank" refers to a number determined by applying any of the formulas to a given siRNA sequence. The term "SMART-selected" or "rationally selected" or "rational selection" refers to siRNA that have been selected on the basis of their SMARTSCORES™, or siRNA ranking.

Substantially Similar

[0125] The phrase "substantially similar" refers to a similarity of at least 90% with respect to the identity of the bases of the sequence.

Target

[0126] The term "target" is used in a variety of different forms throughout this document and is defined by the context in which it is used. "Target mRNA" refers to a messenger RNA to which a given siRNA can be directed against. "Target sequence" and "target site" refer to a sequence within the mRNA to which the sense strand of an siRNA shows varying degrees of homology and the anti-sense strand exhibits varying degrees of complementarity. The phrase "siRNA target" can refer to the gene, mRNA, or protein against which an siRNA is directed. Similarly, "target silencing" can refer to the state of a gene, or the corresponding mRNA or protein.

Transfection

[0127] The term "transfection" refers to a process by which agents are introduced into a cell. The list of agents that can be transfected is large and includes, but is not limited to, siRNA, sense and/or anti-sense sequences, DNA encoding one or more genes and organized into an expression plasmid, proteins, protein fragments, and more. There are multiple methods for transfecting agents into a cell including, but not limited to, electroporation, calcium phosphate-based transfections, DEAE-dextran-based transfections, lipid-based transfections, molecular conjugate-based transfections (e.g., polylysine-DNA conjugates), microinjection and others.

[0128] The present invention is directed to improving the efficiency of gene silencing by siRNA. Through the inclusion of multiple siRNA sequences that are targeted to a particular gene and/or selecting an siRNA sequence based on certain defined criteria, improved efficiency may be achieved.

[0129] The present invention will now be described in connection with preferred embodiments. These embodiments are presented in order to aid in an understanding of the present invention and are not intended, and should not be construed, to limit the invention in any way. All alternatives, modifications and equivalents that may become apparent to those of ordinary skill upon reading this disclosure are included within the spirit and scope of the present invention.

[0130] Furthermore, this disclosure is not a primer on RNA interference. Basic concepts known to persons skilled in the art have not been set forth in detail.

[0131] The present invention is directed to increasing the efficiency of RNAi, particularly in mammalian systems. Accordingly, the present invention provides kits, siRNAs and methods for increasing siRNA efficacy.

[0132] According to a first embodiment, the present invention provides a kit for gene silencing, wherein said kit is comprised of a pool of at least two siRNA duplexes, each of which is comprised of a sequence that is complementary to a portion of the sequence of one or more target messenger RNA, and each of which is selected using non-target specific criteria. Each of the at least two siRNA duplexes of the kit complementary to a portion of the sequence of one or more target mRNAs is preferably selected using Formula X.

[0133] According to a second embodiment, the present invention provides a method for selecting an siRNA, said method comprising applying selection criteria to a set of potential siRNA that comprise 18-30 base pairs, wherein said selection criteria are non-target specific criteria, and said set comprises at least two siRNAs and each of said at least two siRNAs contains a sequence that is at least

substantially complementary to a target gene; and determining the relative functionality of the at least two siRNAs.

[0134] In one embodiment, the present invention also provides a method wherein said selection criteria are embodied in a formula comprising:

$$(-14)*G_{13}-13*A_1-12*U_7-11*U_2-10*A_{11}-10*U_4-10*C_3-10*C_5-10*C_6-9*A_{10}-9*U_9-9*C_{18}-8*G_{10}-7*U_1-7*U_{16}-7*C_{17}-7*C_{19}+7*U_{17}+8*A_2+8*A_4+8*A_5+8*C_4+9*G_8+10*A_7+10*U_{18}+11*A_{19}+11*C_9+15*G_1+18*A_3+19*U_{10}-Tm-3*(GC_{total})-6*(GC_{15-19})-30*X; \text{ or} \quad \text{Formula VIII:}$$

$$(-8)*A1+(-1)*A2+(12)*A3+(7)*A4+(18)*A5+(12)*A6+(19)*A7+(6)*A8+(-4)*A9+(-5)*A10+(-2)*A11+(-5)*A12+(17)*A13+(-3)*A14+(4)*A15+(2)*A16+(8)*A17+(11)*A18+(30)*A19+(-13)*U1+(-10)*U2+(2)*U3+(-2)*U4+(-5)*U5+(5)*U6+(-2)*U7+(-10)*U8+(-5)*U9+(15)*U10+(-1)*U11+(0)*U12+(10)*U13+(-9)*U14+(-13)*U15+(-10)*U16+(3)*U17+(9)*U18+(9)*U19+(7)*C1+(3)*C2+(-21)*C3+(5)*C4+(-9)*C5+(-20)*C6+(-18)*C7+(-5)*C8+(5)*C9+(1)*C10+(2)*C11+(-5)*C12+(-3)*C13+(-6)*C14+(-2)*C15+(-5)*C16+(-3)*C17+(-12)*C18+(-18)*C19+(14)*G1+(8)*G2+(7)*G3+(-10)*G4+(-4)*G5+(2)*G6+(1)*G7+(9)*G8+(5)*G9+(-1)*G10+(1)*G11+(9)*G12+(-24)*G13+(18)*G14+(11)*G15+(13)*G16+(-7)*G17+(-9)*G18+(-22)*G19+6*(\text{number of A+U in position 15-19})-3*(\text{number of G+C in whole siRNA}), \quad \text{Formula X}$$

wherein position numbering begins at the 5'-most position of a sense strand, and

[0135] A_1=1 if A is the base at position 1 of the sense strand, otherwise its value is 0;

[0136] A_2=1 if A is the base at position 2 of the sense strand, otherwise its value is 0;

[0137] A_3=1 if A is the base at position 3 of the sense strand, otherwise its value is 0;

[0138] A_4=1 if A is the base at position 4 of the sense strand, otherwise its value is 0;

[0139] A_5=1 if A is the base at position 5 of the sense strand, otherwise its value is 0;

[0140] A_6=1 if A is the base at position 6 of the sense strand, otherwise its value is 0;

[0141] A_7=1 if A is the base at position 7 of the sense strand, otherwise its value is 0;

[0142] A_{10}=1 if A is the base at position 10 of the sense strand, otherwise its value is 0;

[0143] A_{11}=1 if A is the base at position 11 of the sense strand, otherwise its value is 0;

[0144] A_{13}=1 if A is the base at position 13 of the sense strand, otherwise its value is 0;

[0145] A_{19}=1 if A is the base at position 19 of the sense strand, otherwise if another base is present or the sense strand is only 18 base pairs in length, its value is 0;

[0146] C_3=1 if C is the base at position 3 of the sense strand, otherwise its value is 0;

[0147] C_4=1 if C is the base at position 4 of the sense strand, otherwise its value is 0;

[0148] C_5=1 if C is the base at position 5 of the sense strand, otherwise its value is 0;

[0149] C_6=1 if C is the base at position 6 of the sense strand, otherwise its value is 0;

[0150] C_7=1 if C is the base at position 7 of the sense strand, otherwise its value is 0;

[0151] C_9=1 if C is the base at position 9 of the sense strand, otherwise its value is 0;

[0152] C_{17}=1 if C is the base at position 17 of the sense strand, otherwise its value is 0;

[0153] C_{18}=1 if C is the base at position 18 of the sense strand, otherwise its value is 0;

[0154] C_{19}=1 if C is the base at position 19 of the sense strand, otherwise if another base is present or the sense strand is only 18 base pairs in length, its value is 0;

[0155] G_1=1 if G is the base at position 1 on the sense strand, otherwise its value is 0;

[0156] G_2=1 if G is the base at position 2 of the sense strand, otherwise its value is 0;

[0157] G_8=1 if G is the base at position 8 on the sense strand, otherwise its value is 0;

[0158] G_{10}=1 if G is the base at position 10 on the sense strand, otherwise its value is 0;

[0159] G_{13}=1 if G is the base at position 13 on the sense strand, otherwise its value is 0;

[0160] G_{19}=1 if G is the base at position 19 of the sense strand, otherwise if another base is present or the sense strand is only 18 base pairs in length, its value is 0;

[0161] U_1=1 if U is the base at position 1 on the sense strand, otherwise its value is 0;

[0162] U_2=1 if U is the base at position 2 on the sense strand, otherwise its value is 0;

[0163] U_3=1 if U is the base at position 3 on the sense strand, otherwise its value is 0;

[0164] U_4=1 if U is the base at position 4 on the sense strand, otherwise its value is 0;

[0165] U_7=1 if U is the base at position 7 on the sense strand, otherwise its value is 0;

[0166] U_9=1 if U is the base at position 9 on the sense strand, otherwise its value is 0;

[0167] U_{10}=1 if U is the base at position 10 on the sense strand, otherwise its value is 0;

[0168] U_{15}=1 if U is the base at position 15 on the sense strand, otherwise its value is 0;

[0169] U_{16}=1 if U is the base at position 16 on the sense strand, otherwise its value is 0;

[0170] U_{17}=1 if U is the base at position 17 on the sense strand, otherwise its value is 0;

[0171] U_{18}=1 if U is the base at position 18 on the sense strand, otherwise its value is 0.

[0172] GC_{15-19}=the number of G and C bases within positions 15-19 of the sense strand, or within positions 15-18 if the sense strand is only 18 base pairs in length;

[0173] GC_{total}=the number of G and C bases in the sense strand;

[0174] Tm=100 if the siRNA oligo has the internal repeat longer then 4 base pairs, otherwise its value is 0; and

[0175] X=the number of times that the same nucleotide repeats four or more times in a row.

[0176] Any of the methods of selecting siRNA in accordance with the invention can further comprise comparing the internal stability profiles of the siRNAs to be selected, and selecting those siRNAs with the most favorable internal stability profiles. Any of the methods of selecting siRNA can further comprise selecting either for or against sequences that contain motifs that induce cellular stress. Such motifs include, for example, toxicity motifs. Any of the methods of selecting siRNA can further comprise either selecting for or selecting against sequences that comprise stability motifs.

[0177] In another embodiment, the present invention provides a method of gene silencing, comprising introducing into a cell at least one siRNA selected according to any of the methods of the present invention. The siRNA can be introduced by allowing passive uptake of siRNA, or through the use of a vector.

[0178] According to a third embodiment, the invention provides a method for developing an algorithm for selecting siRNA, said method comprising: (a) selecting a set of siRNA; (b) measuring gene silencing ability of each siRNA from said set; (c) determining relative functionality of each siRNA; (d) determining improved functionality by the presence or absence of at least one variable selected from the group consisting of the presence or absence of a particular nucleotide at a particular position, the total number of As and Us in positions 15-19, the number of times that the same nucleotide repeats within a given sequence, and the total number of Gs and Cs; and (e) developing an algorithm using the information of step (d).

[0179] In another embodiment, the invention provides a method for selecting an siRNA with improved functionality, comprising using the above-mentioned algorithm to identify an siRNA of improved functionality.

[0180] According to a fourth embodiment, the present invention provides a kit, wherein said kit is comprised of at least two siRNAs, wherein said at least two siRNAs comprise a first optimized siRNA and a second optimized siRNA, wherein said first optimized siRNA and said second optimized siRNA are optimized according a formula comprising Formula X.

[0181] According to a fifth embodiment, the present invention provides a method for identifying a hyperfunctional siRNA, comprising applying selection criteria to a set of potential siRNA that comprise 18-30 base pairs, wherein said selection criteria are non-target specific criteria, and said set comprises at least two siRNAs and each of said at least two siRNAs contains a sequence that is at least substantially complementary to a target gene; determining the relative functionality of the at least two siRNAs and assigning each of the at least two siRNAs a functionality score; and selecting siRNAs from the at least two siRNAs that have a functionality score that reflects greater than 80 percent silencing at a concentration in the picomolar range, wherein said greater than 80 percent silencing endures for greater than 120 hours.

[0182] In other embodiments, the invention provides kits and/or methods wherein the siRNA are comprised of two separate polynucleotide strands; wherein the siRNA are comprised of a single contiguous molecule such as, for example, a unimolecular siRNA (comprising, for example, either a nucleotide or non-nucleotide loop); wherein the siRNA are expressed from one or more vectors; and wherein two or more genes are silenced by a single administration of siRNA.

[0183] According to a sixth embodiment, the present invention provides a hyperfunctional siRNA that is capable of silencing Bcl2.

[0184] According to a seventh embodiment, the present invention provides a method for developing an siRNA algorithm for selecting functional and hyperfunctional siRNAs for a given sequence. The method comprises:

[0185] (a) selecting a set of siRNAs;

[0186] (b) measuring the gene silencing ability of each siRNA from said set;

[0187] (c) determining the relative functionality of each siRNA;

[0188] (d) determining the amount of improved functionality by the presence or absence of at least one variable selected from the group consisting of the total GC content, melting temperature of the siRNA, GC content at positions 15-19, the presence or absence of a particular nucleotide at a particular position, relative thermodynamic stability at particular positions in a duplex, and the number of times that the same nucleotide repeats within a given sequence; and

[0189] (e) developing an algorithm using the information of step (d).

[0190] According to this embodiment, preferably the set of siRNAs comprises at least 90 siRNAs from at least one gene, more preferably at least 180 siRNAs from at least two different genes, and most preferably at least 270 and 360 siRNAs from at least three and four different genes, respectively. Additionally, in step (d) the determination is made with preferably at least two, more preferably at least three, even more preferably at least four, and most preferably all of the variables. The resulting algorithm is not target sequence specific.

[0191] In another embodiment, the present invention provides rationally designed siRNAs identified using the formulas above.

[0192] In yet another embodiment, the present invention is directed to hyperfunctional siRNA.

[0193] The ability to use the above algorithms, which are not sequence or species specific, allows for the cost-effective selection of optimized siRNAs for specific target sequences. Accordingly, there will be both greater efficiency and reliability in the use of siRNA technologies.

[0194] The methods disclosed herein can be used in conjunction with comparing internal stability profiles of selected siRNAs, and designing an siRNA with a desirable internal stability profile; and/or in conjunction with a selection either for or against sequences that contain motifs that induce cellular stress, for example, cellular toxicity.

[0195] Any of the methods disclosed herein can be used to silence one or more genes by introducing an siRNA selected, or designed, in accordance with any of the methods dis-

closed herein. The siRNA(s) can be introduced into the cell by any method known in the art, including passive uptake or through the use of one or more vectors.

[0196] Any of the methods and kits disclosed herein can employ either unimolecular siRNAs, siRNAs comprised of two separate polynucleotide strands, or combinations thereof. Any of the methods disclosed herein can be used in gene silencing, where two or more genes are silenced by a single administration of siRNA(s). The siRNA(s) can be directed against two or more target genes, and administered in a single dose or single transfection, as the case may be.

Optimizing siRNA

[0197] According to one embodiment, the present invention provides a method for improving the effectiveness of gene silencing for use to silence a particular gene through the selection of an optimal siRNA. An siRNA selected according to this method may be used individually, or in conjunction with the first embodiment, i.e., with one or more other siRNAs, each of which may or may not be selected by this criteria in order to maximize their efficiency.

[0198] The degree to which it is possible to select an siRNA for a given mRNA that maximizes these criteria will depend on the sequence of the mRNA itself. However, the selection criteria will be independent of the target sequence. According to this method, an siRNA is selected for a given gene by using a rational design. That said, rational design can be described in a variety of ways. Rational design is, in simplest terms, the application of a proven set of criteria that enhance the probability of identifying a functional or hyperfunctional siRNA. In one method, rationally designed siRNA can be identified by maximizing one or more of the following criteria:

[0199] (1) A low GC content, preferably between about 30-52%.

[0200] (2) At least 2, preferably at least 3 A or U bases at positions 15-19 of the siRNA on the sense strand.

[0201] (3) An A base at position 19 of the sense strand.

[0202] (4) An A base at position 3 of the sense strand.

[0203] (5) A U base at position 10 of the sense strand.

[0204] (6) An A base at position 14 of the sense strand.

[0205] (7) A base other than C at position 19 of the sense strand.

[0206] (8) A base other than G at position 13 of the sense strand.

[0207] (9) A Tm, which refers to the character of the internal repeat that results in inter- or intramolecular structures for one strand of the duplex, that is preferably not stable at greater than 50° C., more preferably not stable at greater than 37° C., even more preferably not stable at greater than 30° C. and most preferably not stable at greater than 20° C.

[0208] (10) A base other than U at position 5 of the sense strand.

[0209] (11) A base other than A at position 11 of the sense strand.

[0210] (12) A base other than an A at position 1 of the sense strand.

[0211] (13) A base other than an A at position 2 of the sense strand.

[0212] (14) An A base at position 4 of the sense strand.

[0213] (15) An A base at position 5 of the sense strand.

[0214] (16) An A base at position 6 of the sense strand.

[0215] (17) An A base at position 7 of the sense strand.

[0216] (18) An A base at position 8 of the sense strand.

[0217] (19) A base other than an A at position 9 of the sense strand.

[0218] (20) A base other than an A at position 10 of the sense strand.

[0219] (21) A base other than an A at position 11 of the sense strand.

[0220] (22) A base other than an A at position 12 of the sense strand.

[0221] (23) An A base at position 13 of the sense strand.

[0222] (24) A base other than an A at position 14 of the sense strand.

[0223] (25) An A base at position 15 of the sense strand

[0224] (26) An A base at position 16 of the sense strand.

[0225] (27) An A base at position 17 of the sense strand.

[0226] (28) An A base at position 18 of the sense strand.

[0227] (29) A base other than a U at position 1 of the sense strand.

[0228] (30) A base other than a U at position 2 of the sense strand.

[0229] (31) A U base at position 3 of the sense strand.

[0230] (32) A base other than a U at position 4 of the sense strand.

[0231] (33) A base other than a U at position 5 of the sense strand.

[0232] (34) A U base at position 6 of the sense strand.

[0233] (35) A base other than a U at position 7 of the sense strand.

[0234] (36) A base other than a U at position 8 of the sense strand.

[0235] (37) A base other than a U at position 9 of the sense strand.

[0236] (38) A base other than a U at position 11 of the sense strand.

[0237] (39) A U base at position 13 of the sense strand.

[0238] (40) A base other than a U at position 14 of the sense strand.

[0239] (41) A base other than a U at position 15 of the sense strand.

[0240] (42) A base other than a U at position 16 of the sense strand.

[0241] (43) A U base at position 17 of the sense strand.

[0242] (44) A U base at position 18 of the sense strand.

[0243] (45) A U base at position 19 of the sense strand.

[0244] (46) A C base at position 1 of the sense strand.

[0245] (47) A C base at position 2 of the sense strand.

[0246] (48) A base other than a C at position 3 of the sense strand.

[0247] (49) A C base at position 4 of the sense strand.

[0248] (50) A base other than a C at position 5 of the sense strand.

[0249] (51) A base other than a C at position 6 of the sense strand.

[0250] (52) A base other than a C at position 7 of the sense strand.

[0251] (53) A base other than a C at position 8 of the sense strand.

[0252] (54) A C base at position 9 of the sense strand.

[0253] (55) A C base at position 10 of the sense strand.

[0254] (56) A C base at position 11 of the sense strand.

[0255] (57) A base other than a C at position 12 of the sense strand.

[0256] (58) A base other than a C at position 13 of the sense strand.

[0257] (59) A base other than a C at position 14 of the sense strand.

[0258] (60) A base other than a C at position 15 of the sense strand.

[0259] (61) A base other than a C at position 16 of the sense strand.

[0260] (62) A base other than a C at position 17 of the sense strand.

[0261] (63) A base other than a C at position 18 of the sense strand.

[0262] (64) A G base at position 1 of the sense strand.

[0263] (65) A G base at position 2 of the sense strand.

[0264] (66) A G base at position 3 of the sense strand.

[0265] (67) A base other than a G at position 4 of the sense strand.

[0266] (68) A base other than a G at position 5 of the sense strand.

[0267] (69) A G base at position 6 of the sense strand.

[0268] (70) A G base at position 7 of the sense strand.

[0269] (71) A G base at position 8 of the sense strand.

[0270] (72) A G base at position 9 of the sense strand.

[0271] (73) A base other than a G at position 10 of the sense strand.

[0272] (74) A G base at position 11 of the sense strand.

[0273] (75) A G base at position 12 of the sense strand.

[0274] (76) A G base at position 14 of the sense strand.

[0275] (77) A G base at position 15 of the sense strand.

[0276] (78) A G base at position 16 of the sense strand.

[0277] (79) A base other than a G at position 17 of the sense strand.

[0278] (80) A base other than a G at position 18 of the sense strand.

[0279] (81) A base other than a G at position 19 of the sense strand.

[0280] The importance of various criteria can vary greatly. For instance, a C base at position 10 of the sense strand makes a minor contribution to duplex functionality. In contrast, the absence of a C at position 3 of the sense strand is very important. Accordingly, preferably an siRNA will satisfy as many of the aforementioned criteria as possible.

[0281] With respect to the criteria, GC content, as well as a high number of AU in positions 15-19 of the sense strand, may be important for easement of the unwinding of double stranded siRNA duplex. Duplex unwinding has been shown to be crucial for siRNA functionality in vivo.

[0282] With respect to criterion 9, the internal structure is measured in terms of the melting temperature of the single strand of siRNA, which is the temperature at which 50% of the molecules will become denatured. With respect to criteria 2-8 and 10-11, the positions refer to sequence positions on the sense strand, which is the strand that is identical to the mRNA.

[0283] In one preferred embodiment, at least criteria 1 and 8 are satisfied. In another preferred embodiment, at least criteria 7 and 8 are satisfied. In still another preferred embodiment, at least criteria 1, 8 and 9 are satisfied.

[0284] It should be noted that all of the aforementioned criteria regarding sequence position specifics are with respect to the 5' end of the sense strand. Reference is made to the sense strand, because most databases contain information that describes the information of the mRNA. Because according to the present invention a chain can be from 18 to 30 bases in length, and the aforementioned criteria assumes a chain 19 base pairs in length, it is important to keep the aforementioned criteria applicable to the correct bases.

[0285] When there are only 18 bases, the base pair that is not present is the base pair that is located at the 3' of the sense strand. When there are twenty to thirty bases present, then additional bases are added at the 5' end of the sense chain and occupy positions $^{-}1$ to $^{-}11$. Accordingly, with respect to SEQ. ID NO. 0001 NNANANNNNUCNAANNNNA and SEQ. ID NO. 0028 GUCNNANANNNNUCNAANNNNA, both would have A at position 3, A at position 5, U at position 10, C at position 11, A and position 13, A and position 14 and A at position 19. However, SEQ. ID NO. 0028 would also have C at position −1, U at position −2 and G at position −3.

[0286] For a 19 base pair siRNA, an optimal sequence of one of the strands may be represented below, where N is any base, A, C, G, or U:

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nnanannnnu cnaannnna 19

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nnanannnnu gnaannnna 19

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nnanannnnu unaannnna 19

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nnancnnnnu cnuannnna 19

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aggggagatg gcacaggagg aaagagcatc tacggtgagc gcttccccga tgagaacttc 180

aaactgaagc actacgggcc tggctggg 208

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cgtggattac gtcgccagtc aagtaacaac cgcgaaaaag ttgcgcggag gagttgtgtt 120

tgtggacgaa gtaccgaaag gtcttaccgg aaaactcgac gcaagaaaaa tcagagagat 180

cctcataaag gccaagaagg 200

<210> SEQ ID NO 31
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<220> FEATURE:
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<222> LOCATION: (1)...(108)
<223> OTHER INFORMATION: Human DBL fragment

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atgaaagctt acatcaacaa agtagaagag ctaaagaaaa aatacggg 108

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guuccaaaaa caguggaua 19

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uccaaaaaca guggauaau 19

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caaaaacagu ggauaauuu 19

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aaaacagugg auaauuuug 19

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aacaguggau aauuuugug 19

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caguggauaa uuuuguggc 19

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guggauaauu uuguggccu 19

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ggauaauuuu guggccuua 19

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aauuuugugg ccuuagcua 19

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uuuuguggcc uuagcuaca 19

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uuguggccuu agcuacagg 19

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guggccuuag cuacaggag 19

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ggccuuagcu acaggagag 19

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ccuuagcuac aggagagaa 19

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uuagcuacag gagagaaag 19

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agcuacagga gagaaagga 19

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cuacaggaga gaaaggauu 19

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acaggagaga aaggauuug 19

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aggagagaaa ggauuuggc 19

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gagagaaagg auuuggcua 19

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gagaaaggau uuggcuaca 19

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gaaaggauuu ggcuacaaa 19

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aaggauuugg cuacaaaaa 19

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ggauuuggcu acaaaaaca 19

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auuuggcuac aaaaacagc 19

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uuggcuacaa aaacagcaa 19

<210> SEQ ID NO 59
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ggcuacaaaa acagcaaau 19

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cuacaaaaac agcaaauuc 19

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acaaaaacag caaauucca 19

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aaaaacagca aauuccauc 19

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aaacagcaaa uuccaucgu 19

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acagcaaauu ccaucgugu 19

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agcaaauucc aucguguaa 19

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caaauuccau cguguaauc 19

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aauuccaucg uguaaucaa 19

<210> SEQ ID NO 68
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uuccaucgug uaaucaagg 19

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ccaucgugua aucaaggac 19

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aucguguaau caaggacuu 19

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cguguaauca aggacuuca 19

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uguaaucaag gacuucaug 19

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uaaucaagga cuucaugau 19

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aucaaggacu ucaugaucc 19

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caaggacuuc augauccag 19

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aggacuucau gauccaggg 19

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gacuucauga uccagggcg 19

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cuucaugauc cagggcgga 19

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ucaugaucca gggcggaga 19

<210> SEQ ID NO 80
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augauccagg gcggagacu 19

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gauccagggc ggagacuuc 19

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uccagggcgg agacuucac 19

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cagggcggag acuucacca 19

<210> SEQ ID NO 84
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gcggagacuu caccagggg 19

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ggagacuuca ccaggggag 19

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agacuucacc aggggagau 19

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acuucaccag gggagaugg 19

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aggggagaug gcacaggag 19

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gagauggcac aggaggaaa 19

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gauggcacag gaggaaaga 19

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uggcacagga ggaaagagc 19

<210> SEQ ID NO 97
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<213> ORGANISM: Artificial Sequence
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gcacaggagg aaagagcau 19

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aggaggaaag agcaucuac 19

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ggaaagagca ucuacggug 19

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aaagagcauc uacggugag 19

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caucuacggu gagcgcuuc 19

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ucuacgguga gcgcuuccc 19

<210> SEQ ID NO 107
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gugagcgcuu ccccgauga 19

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gagcgcuucc ccgaugaga 19

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gcgcuucccc gaugagaac 19

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gcuuccccga ugagaacuu 19

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ccccgaugag aacuucaaa 19

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ccgaugagaa cuucaaacu 19

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gaugagaacu ucaaacuga 19

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ugagaacuuc aaacugaag 19

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agaacuucaa acugaagca 19

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aacuucaaac ugaagcacu 19

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cuucaaacug aagcacuac 19

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<210> SEQ ID NO 122
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cgggcaaggc caaguggga 19

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gggcaaggcc aagugggau 19

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cugaaaggga cuuccaagg 19

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agggacuucc aaggaagau 19

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gggacuucca aggaagaug 19

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gaugccauga aagcuuaca 19

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augccaugaa agcuuacau 19

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gaaagcuuac aucaacaaa 19

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cuuacaucaa caaaguaga 19

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uuacaucaac aaaguagaa 19

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caucaacaaa guagaagag 19

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aucaacaaag uagaagagc 19

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caacaaagua gaagagcua 19

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aacaaaguag aagagcuaa 19

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acaaaguaga agagcuaaa 19

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aaucagagag auccucaua 19

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aaaguugcgc ggaggaguu 19

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gucgccaguc aaguaacaa 19

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gcacggaaag acgaugacg 19

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guuguuguuu uggagcacg 19

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cgccguuguu guuuuggag 19

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gccgccguug uuguuuugg 19

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ccgccgccgu uguuguuuu 19

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agauagugau gaaguacau 19

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ugaagacucu gcucaguuu 19

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gagauaguga ugaaguaca 19

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tgacaaaggt ggataaatt 19

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gaaggtggcc cagctatgt 19

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gaaatggaac cactaagaa 19

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ggaaatggaa ccactaaga 19

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caactacact ttccaatgc 19

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ccaccaagat ttcatgata 19

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gatcggaact ccaacaaga 19

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aaacggagct acagattat 19

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ccacacagca ttcttgtaa 19

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gaagttacct tgagcaatc 19

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ggacttggcc gatccagaa 19

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gcacttggat cgagatgag 19

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caaagaccaa ttcgcgtta 19

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ccgaatcaat cgcatcttc 19

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gacatgatcc tgcagttca 19

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gagcgaatcg tcaccactt 19

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gatgagggac gccataatc 19

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cctctaacta caaatctta 19

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ggaaggtgct atccaaaat 19

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gcaagcaagt cctaacatt 19

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ggaagaggag tagacctta 19

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aggaatcagt gttgtagta 19

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gaagaggagt agaccttac 19

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caagcctggt attacgttt 19

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ggaacaagat ctgtcaatt 19

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gcaatgaacg tgaacgaaa 19

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caatgaacgt gaacgaaat 19

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ggacaggagc ggtatcaca 19

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agacagagct tgagaataa 19

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gagaagatct ttatgcaaa 19

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gaagagaaat cagcagata 19

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gcaagtaact caactaaca 19

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gagctaatct gccacattg 19

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gcagatgagt tactagaaa 19

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caacttaatt gtccagaaa 19

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caacacagga ttctgataa 19

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agattgtgcc taagtctct 19

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atgaagatct ggaggtgaa 19

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tttgagactt cttgcctaa 19

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agatcaccct ccttaaata 19

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caacggattt ggtcgtatt 19

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gaaatcccat caccatctt 19

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gacctcaact acatggttt 19

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tggtttacat gttccaata 19

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gaagaaatcg atgttgttt 19

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acacaaactt gaacagcta 19

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ggaagaaatc gatgttgtt 19

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gaaacgacga gaacagttg 19

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gcacatggat ggaggttct 19

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gcagagagag cagatttga 19

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gaggttctct ggatcaagt 19

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gagcagattt gaagcaact 19

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caaagacgat gacttcgaa 19

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gatcagcatt tgcatggaa 19

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tccaggagtt tgtcaataa 19

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ggaagctgat ccaccttga 19

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gcagaaatct aaggatata 19

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caacaaggat gaagtctat 19

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cagcagaaat ctaaggata 19

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ctagatggct ttctcagta 19

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agacaaggtc ccaaagaca 19

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ggaatggcaa gaccagcaa 19

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agaattattc cagggttta 19

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gcagacaagg tcccaaaga 19

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agaagcagct tcaggatga 19

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gagcttgact tccagaaga 19

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ccaccgaagt tcaccctaa 19

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gagaagagct cctccatca 19

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gaaagagcat ctacggtga 19

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gaaaggattt ggctacaaa 19

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acagcaaatt ccatcgtgt 19

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ggaaagactg ttccaaaaa 19

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caacacgcct catcctcta 19

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aagatgccat gaaagctta 19

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gcacataccg cctgagtct 19

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gatcaaatct gaagaagga 19

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gccaagaagt ttcctaata 19

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cagcatatct tgaaccatt 19

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gaacaaagga aacggatga 19

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cggaaacggt ccaggctat 19

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gcttcgagca gacatgata 19

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cctacacggt cctcctata 19

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gccaagaacc tcatcatct 19

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gatatgggct gaatacaaa 19

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gcactctgat tgacaaata 19

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tgaagtctct gattaagta 19

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tcagagagat cctcataaa 19

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gcaagaagat caccatttc 19

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gagagaaatt tgaggatga 19

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gaaaggattt ggctataag 19

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gaaagaaggc atgaacatt 19

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gggagatagt gatgaagta 19

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gaagtacatc cattataag 19

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gtacgacaac cgggagata 19

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tgaagactct gctcagttt 19

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gcacacagcu uacuacauc 19

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gaaaugcccu gguaucuca 19

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gaaggaacgu gaugugauc 19

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gcacuacucc ugugugga 19

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gauauacagu gugaucuua 19

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guacuacgau ccugauuau 19

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gugccgaccu uuacaauuu 19

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agaagacugu uaaagcaaa 19

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cagaguuugu guguauuug 19

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cagaugaaug cggcuguua 19

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ccaugggaau ccaaucugu 19

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cugcaauaau ccagaaugg 19

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gaagacuguu aaagcaaaa 19

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gaauggcuac ucugaucua 19

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gaguuugugu guauuugua 19

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gaucuauguu gauaaggaa 19

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gaugaaugcg gcuguuaag 19

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gaugaugccu auccagaaa 19

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ggagaucuca aguuucaac 19

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guuaagaccu gcaauaauc 19

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guugaauugc caccuguuu 19

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uaaagcauuc uucaacaga 19

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ucagaguuug uguguauuu 19

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ucugaucuau guugauaag 19

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ucuuagugcu ucagaguuu 19

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ugaaugcggc uguuaagac 19

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ugacgaggag agagagcuu 19

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ugacugagaa gacuguuaa 19

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ugagaagacu guuaaagca 19

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ugauaaggaa aauggagaa 19

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ugaucuaugu ugauaagga 19

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ugaugccuau ccagaaaua 19

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uggagugccu cucaugauc 19

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uggcuacucu gaucuaugu 19

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ugggagaucu caaguuuca 19

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uuaccuaaag cuacuagaa 19

We claim:

1. An siRNA comprising a sense region and an antisense region, wherein said sense region and said antisense region together form a duplex region, said antisense region and said sense region are each 18-30 nucleotides in length and said antisense region comprises a sequence that is at least 90% complementary to a sequence selected from the group consisting of SEQ. ID NOs. 438-498.

2. An siRNA comprising a sense region and an antisense region, wherein said sense region and said antisense region together form a duplex region and said sense region and said antisense region are each 18-30 nucleotides in length, and said antisense region comprises a sequence that is 100% complementary to a contiguous stretch of at least 18 bases of a sequence selected from the group consisting of SEQ. ID NOs. 438-498.

3. The siRNA of claim 2, wherein each of said antisense region and said sense region are 19-30 nucleotides in length, and said antisense region comprises a sequence that is 100% complementary to said sequence selected from the group consisting of: SEQ. ID NOs. 438-498.

4. A pool of at least two siRNAs, wherein said pool comprises a first siRNA and a second siRNA, said first siRNA comprises a first antisense region and a first sense region that together form a first duplex region and each of said first antisense region and said first sense region are 18-30 nucleotides in length and said first antisense region is at least 90% complementary to 18 bases of a first sequence selected from the group consisting of: SEQ. ID NOs. 438-498 and said second siRNA comprises a second antisense region and a second sense region that together form a second duplex region and each of said second antisense region and said second sense region are 18-30 nucleotides in length and said second antisense region is at least 90% complementary to 18 bases of a second sequence selected from the group consisting of: SEQ. ID NOs. 438-498, wherein said first antisense region and said second antisense region are not identical.

5. The pool of claim 4, wherein said first antisense region comprises a sequence that is 100% complementary to at least 18 bases of said first sequence, and said second antisense region comprises a sequence that is 100% complementary to at least 18 bases of said second sequence.

6. The pool of claim 4, wherein said first siRNA is 19-30 nucleotides in length and said first antisense region comprises a sequence that is at least 90% complementary to said first sequence, and second siRNA is 19-30 nucleotides in length and said second antisense region comprises a sequence that is at least 90% complementary to said second sequence.

7. The pool of claim 4, wherein said first antisense region is 19-30 nucleotides in length and said first antisense region comprises a sequence that is 100% complementary to at least 18 bases of said first sequence, and said second antisense region is 19-30 nucleotides in length and said second antisense region comprises a sequence that is 100% complementary to said second sequence.

8. The siRNA of claim 1, wherein said antisense region and said sense region are each 19-25 nucleotides in length.

9. The siRNA of claim 4, wherein said first antisense region, said first sense region, said second sense region and said second antisense region are each 19-25 nucleotides in length.

* * * * *