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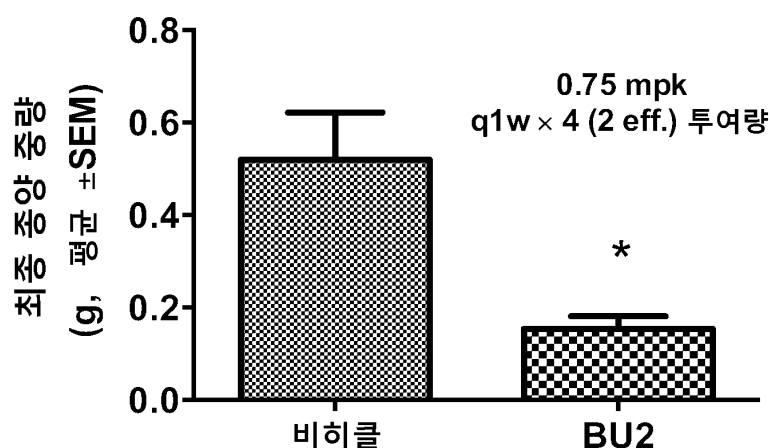
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(54) 발명의 명칭 GST-PI 유전자 조절을 위한 RNA 제제

(57) 요약

본 발명은 RNA 간섭을 사용하는 인간 GST- π 의 발현을 조절하기 위한 화합물, 조성물 및 방법을 제공한다. RNA 간섭 분자는 악성 종양과 같은 질환을 예방 또는 치료하기 위한 방법에서 사용될 수 있다. 핵산 분자는 a) 폴리뉴클레오타이드 센스 가닥 및 폴리뉴클레오타이드 안티센스 가닥을 가질 수 있고; b) 분자의 각각의 가닥은 15 내지 30 개 뉴클레오타이드 길이이고; c) 안티센스 가닥의 15 내지 30 개 뉴클레오타이드의 인접 영역은 GST- π 를 인코딩하는 mRNA의 서열에 상보적이고; d) 센스 가닥의 적어도 일부는 안티센스 가닥의 적어도 일부에 상보적일 수 있고, 분자는 15 내지 30 개 뉴클레오타이드 길이의 듀플렉스 영역을 갖는다.

대표도 - 도4



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명세서

청구범위

청구항 1

하기와 같은 핵산 분자:

- a) 분자는 폴리뉴클레오티드 센스 가닥 및 폴리뉴클레오티드 안티센스 가닥을 가짐;
- b) 분자의 각각의 가닥은 15 내지 30 개 뉴클레오티드 길이임;
- c) 안티센스 가닥의 15 내지 30 개 뉴클레오티드의 인접 영역은 GST- π 를 인코딩하는 mRNA 의 서열과 상보적임;
- d) 센스 가닥의 적어도 일부는 안티센스 가닥의 적어도 일부에 상보적이고, 분자는 15 내지 30 개 뉴클레오티드 길이의 듀플렉스 영역을 가짐.

청구항 2

제 1 항에 있어서, 안티센스 가닥이 SEQ ID NO:1341 이고, 센스 가닥이 SEQ ID NO:1276 이거나, 또는 이의 화학적으로 개질된 가닥인 핵산 분자.

청구항 3

제 1 항에 있어서, 안티센스 가닥이 SEQ ID NO:1305 이고, 센스 가닥이 SEQ ID NO:1240 이거나, 또는 이의 화학적으로 개질된 가닥인 핵산 분자.

청구항 4

제 1 항에 있어서, GST- π 를 인코딩하는 mRNA 의 서열에 상보적인 안티센스 가닥의 15 내지 30 개 뉴클레오티드의 인접 영역이 분자의 듀플렉스 영역에 위치하는 핵산 분자.

청구항 5

제 1 항에 있어서, GST- π 를 인코딩하는 mRNA 의 서열에 상보적인 안티센스 가닥의 15 내지 30 개 뉴클레오티드의 인접 영역이 인간 GSTP1 의 서열로부터 선택되고, 인간 GSTP1 mRNA 가 SEQ ID NO:1 인 핵산 분자.

청구항 6

제 1 항에 있어서, GST- π 를 인코딩하는 mRNA 의 서열이 SEQ ID NO:1 의 5'UTR 위치 1 내지 249, SEQ ID NO:1 의 CDS 위치 250 내지 882, 및 SEQ ID NO:1 의 3'UTR 위치 883 내지 986 으로 이루어지는 군으로부터 선택되는 핵산 분자.

청구항 7

제 1 항에 있어서, 안티센스 가닥이 SEQ ID NO:609-1215 중 어느 하나로부터 선택되는 서열을 함유하는 핵산 분자.

청구항 8

제 1 항에 있어서, 안티센스 가닥이 SEQ ID NO:1281-1345 중 어느 하나로부터 선택되는 서열을 함유하는 핵산 분자.

청구항 9

제 1 항에 있어서, 분자가 SEQ ID NO:1240 및 1305, SEQ ID NO:1265 및 1330, SEQ ID NO:1267 및 1332, SEQ ID NO:1269 및 1334, 및 SEQ ID NO:1276 및 1341 로 이루어지는 군으로부터 선택되는 안티센스 및 센스 가닥 쌍으로 구성되는 핵산 분자.

청구항 10

제 1 항에 있어서, 분자의 각각의 가닥이 18 내지 22 개 뉴클레오티드 길이인 핵산 분자.

청구항 11

제 1 항에 있어서, 듀플렉스 영역이 19 개 뉴클레오티드 길이인 핵산 분자.

청구항 12

제 1 항에 있어서, 폴리뉴클레오티드 센스 가닥 및 폴리뉴클레오티드 안티센스 가닥이 단일 가닥으로서 연결되고, 루프에 의해 하나의 말단에서 연결된 듀플렉스 영역을 형성하는 핵산 분자.

청구항 13

제 1 항에 있어서, 분자가 블런트 말단을 갖는 핵산 분자.

청구항 14

제 1 항에 있어서, 분자가 하나 이상의 3' 오버행을 갖는 핵산 분자.

청구항 15

제 1 항에 있어서, 분자가 유전자 침묵화에 활성인 RNAi 분자인 핵산 분자.

청구항 16

제 1 항에 있어서, 분자가 유전자 침묵화에 활성인 dsRNA, siRNA, 마이크로-RNA, 또는 shRNA 인 핵산 분자.

청구항 17

제 1 항에 있어서, 분자가 GST- π 의 발현 억제에 활성인 핵산 분자.

청구항 18

제 1 항에 있어서, 분자가 100 pM 미만의 GST- π 의 녹다운에 대한 IC50 을 갖는 핵산 분자.

청구항 19

제 1 항 내지 제 18 항 중 어느 한 항의 핵산 분자 하나 이상 및 약학적으로 허용가능한 담체를 포함하는 조성물.

청구항 20

제 19 항에 있어서, 담체가 지질 분자 또는 리포솜인 조성물.

청구항 21

GST- π 발현과 연관된 질환의 치료 방법으로서, 제 19 항의 조성물을 이를 필요로 하는 대상체에게 투여하는 것을 포함하는 방법.

청구항 22

제 21 항에 있어서, 질환이 악성 종양인 방법.

청구항 23

제 22 항에 있어서, 악성 종양이 GST- π 발현과 연관된 암, 돌연변이된 KRAS 를 발현하는 세포에 의해 야기되는 암, 육종, 섬유육종, 악성 섬유 조직구종, 지방육종, 횡문근육종, 평활근육종, 혈관육종, 카포시 육종, 림프관육종, 활액막 육종, 연골육종, 골육종, 암종, 뇌종양, 두경부암, 유방암, 폐암, 식도암, 위암, 십이지장암, 결장직장암, 결장암, 간암, 췌장암, 담낭암, 담관암, 신장암, 요도암, 방광암, 전립선암, 고환암, 음경암, 자궁암, 난소암, 피부암, 뼈암, 백혈병, 악성 림프종, 상피성 악성 종양, 및 비-상피성 악성 종양으로 이루어지

는 군으로부터 선택되는 질환에 존재하는 방법.

발명의 설명

기술 분야

[0001] 발명의 기술 분야

[0002] 본 발명은 핵산 기반 분자로 구성되는 생물의약품 및 치료제의 분야와 관련된다. 더 상세하게는, 본 발명은 인간 GST- π 의 발현을 조정하기 위해 RNA 간섭 (RNA interference) (RNAi)을 이용하는 화합물 및 조성물과 관련된다.

[0003] 서열목록

[0004] 본 출원은 2015년 12월 23일에 생성된 ASCII 파일로서 전자적으로 제출되는 파일명이 ND5123202WO_SL.txt인 서열 목록을 포함하고, 그 크기는 442,955 바이트이고, 여기에 그 전체가 참조로서 인용된다.

배경 기술

[0005] 다양한 인간 암 조직은 돌연변이된 KRAS 유전자의 출현과 상관관계가 있는 것으로 밝혀졌다. 일부 경우, 조직은 또한 상승된 수준의 글루타티온 S-트랜스퍼라제 Pi (Glutathione S-Tranferase Pi) (GST- π) 발현을 나타낸다. (Miyaniishi et al., Gastroenterology, 2001, Vol. 121:865-874, Abstract) 예를 들어, 상승된 혈청 GST- π 수준이 다양한 위장 악성종양을 가진 환자에서 관찰되었다. (Niitsu et al., Cancer, 1989, Vol.63, No. 2, pp. 317-323, Abstract)

[0006] GST- π 는 소수성 및 친전자성 화합물과 환원된 글루타티온과의 공유결합을 촉매작용함으로써 해독에 역할을 하는 효소의 GST 패밀리의 구성원이다. GST- π 발현은 siRNA로 시험관 내에서 감소될 수 있다. (Niitsu et al., US 2014/0315975 A1)

발명의 내용

해결하려는 과제

[0007] GST- π 발현의 억제를 위한 치료학은 고도로 강력한 siRNA 서열 및 구조를 필요로 할 것이다.

[0008] 필요한 것은 GST- π 발현의 억제를 위한 siRNA 서열, 화합물 및 구조이다.

과제의 해결 수단

[0009] 본 발명은 RNA 간섭을 사용하여 인간 GST- π 의 발현을 조정하기 위한 화합물, 조성물 및 방법에 관한 것이다.

[0010] 일부 구현예에서, 본 발명은 GST- π 의 RNA 간섭 유전자 침묵화 (gene silencing)를 위한 분자를 제공한다.

[0011] 추가의 구현예에서, 본 발명의 구조, 분자 및 조성물은 질환을 예방 또는 치료하기 위한, 또는 악성 종양을 포함하는, GST- π 와 연관된 조건 또는 장애의 증상을 경감하기 위한 방법에서 사용될 수 있다.

[0012] 본 발명의 구현예는 하기를 포함한다:

[0013] 하기와 같은 핵산 분자:

[0014] a) 분자는 폴리뉴클레오티드 센스 가닥 및 폴리뉴클레오티드 안티센스 가닥을 가짐;

[0015] b) 분자의 각각의 가닥은 15 내지 30 개 뉴클레오티드 길이임;

[0016] c) 안티센스 가닥의 15 내지 30의 뉴클레오티드의 인접 영역은 GST- π 를 인코딩하는 mRNA의 서열과 상보적임;

[0017] d) 센스 가닥의 적어도 일부는 안티센스 가닥의 적어도 일부에 상보적이고, 상기 분자는 15 내지 30 개 뉴클레오티드 길이의 듀플렉스 영역을 가짐.

- [0018] 일부 구현예에서, 핵산 분자는 분자의 듀플렉스 영역 내에 위치하는 GST- π 를 인코딩하는 mRNA 의 서열에 상보적인 안티센스 가닥의 15 내지 30 개 뉴클레오타이드의 인접 영역을 가질 수 있다.
- [0019] 부가적인 구현예에서, 핵산 분자는 GST- π 를 인코딩하는 mRNA 의 서열에 상보적인 안티센스 가닥의 15 내지 30 개 뉴클레오타이드의 인접 영역을 가질 수 있다.
- [0020] 본 발명의 화합물은 SEQ ID NO:1 의 5'UTR 위치 1 내지 249, SEQ ID NO:1 의 CDS 위치 250 내지 882, 및 SEQ ID NO:1 의 3'UTR 위치 883 내지 986 으로 이루어지는 군으로부터 선택되는 GST- π 를 인코딩하는 mRNA 의 서열을 가질 수 있다.
- [0021] 특정 구현예에서, 핵산 분자의 각각의 가닥은 18 내지 22 개 뉴클레오타이드 길이일 수 있다. 핵산 분자의 듀플렉스 영역은 19 개 뉴클레오타이드 길이일 수 있다.
- [0022] 대안적인 형태에서, 핵산 분자는 단일 가닥으로서 연결된 폴리뉴클레오타이드 센스 가닥 및 폴리뉴클레오타이드 안티센스 가닥을 가질 수 있고, 루프에 의해 하나의 말단에 연결된 듀플렉스 영역을 형성한다.
- [0023] 본 설명의 핵산 분자의 일부 구현예는 블런트 말단을 가질 수 있다. 특정 구현예에서, 핵산 분자는 하나 이상의 3' 오버행 (overhang) 을 가질 수 있다.
- [0024] 본 발명은 유전자 침묵화를 위해 활성인 RNAi 분자인 다양한 핵산 분자를 제공한다. 본 발명의 핵산 분자는 유전자 침묵화를 위해 활성인 dsRNA, siRNA, 마이크로-RNA, 또는 shRNA, 뿐 아니라 DNA-지정 RNA (ddRNA), Piwi-상호작용 RNA (piRNA), 또는 반복 연관 siRNA (rasiRNA) 일 수 있다. 핵산 분자는 GST- π 의 발현 억제를 위해 활성일 수 있다.
- [0025] 본 발명의 구현예는 추가로 100 pM 미만의 GST- π 의 녹다운 (knockdown) 을 위한 IC50 을 갖는 핵산 분자를 제공한다.
- [0026] 본 발명은 추가로 본 발명의 핵산 분자 중 하나 이상을, 약학적으로 허용가능한 담체와 함께 함유하는 조성물을 고려한다. 특정 구현예에서, 담체는 지질 분자 또는 리포솜일 수 있다.
- [0027] 본 발명의 화합물 및 조성물은 화합물 또는 조성물을 이를 필요로 하는 대상체에게 투여함으로써, GST- π 관련 질환을 예방 또는 치료하기 위한 방법에서 유용하다.
- [0028] 본 발명의 방법은 악성 종양을 예방 또는 치료하기 위해 본 발명의 화합물을 이용할 수 있다. 악성 종양은 다양한 질환, 예를 들어, GST- π 발현과 연관된 암, 돌연변이된 KRAS 를 발현하는 세포에 의해 야기되는 암, 육종, 섬유육종, 악성 섬유 조직구종, 지방육종, 횡문근육종, 평활근육종, 혈관육종, 카포시 육종, 림프관 육종, 활액막 육종, 연골육종, 골육종, 암종, 뇌종양, 두경부암, 유방암, 폐암, 식도암, 위암, 십이지장암, 맹장암, 결장직장암, 직장암, 간암, 췌장암, 담낭암, 담관암, 항문암, 신장암, 요도암, 방광암, 전립선암, 고환암, 자궁암, 난소암, 피부암, 백혈병, 악성 림프종, 상피성 악성 종양, 및 비-상피성 악성 종양에 존재할 수 있다.

도면의 간단한 설명

- [0029] 도 1: 도 1 은 SEQ ID NO: 1 을 보여주며, 이것은 986 개 뉴클레오타이드 길이인, GenBank 수탁 번호 NM_000852.3 (hGSTP1) 에 기재된, 표적 인간 글루타티온 S -트랜스페라아제 pi (인간 GST- π) mRNA 의 핵산 서열이다.
- 도 2: 도 2 는 GST- π siRNA 에 대한 생체 내 녹다운 효력을 보여준다. GST- π mRNA 의 용량 의존적 녹다운을 도 2 에 제시된 바와 같이, GST- π 에 표적한 siRNA 와 함께 생체 내에서 관찰하였다.
- 도 3: 도 3 은 GST- π siRNA 에 의한 증식의 억제를 보여준다. 증식의 투여량-의존적 억제를 도 3 에 제시된 바와 같이, GST- π 에 표적한 siRNA 와 함께 시험관 내에서 A549 세포주에서 관찰하였다.
- 도 4: 도 4 는 GST- π siRNA 에 대한 종양 억제 효과를 보여준다. 췌장암 이종이식 모델은 GST- π 에 표적한 siRNA 의 0.75 mg/kg 에서 비교적 낮은 투여량으로 이용하였다. GST- π siRNA 는 유효한 종양 억제 효과를 입증하였다.

발명을 실시하기 위한 구체적인 내용

- [0030] 본 발명은 GST- π 의 발현을 조정하기 위한 핵산 기반의 치료법을 위한 화합물, 조성물 및 방법에 관한 것이다.

- [0031] 일부 구현예에서, 본 발명은 RNA 간섭에 활성인 분자 뿐 아니라, GST- π 의 발현을 침묵시킬 수 있는 구조 및 조성물을 제공한다.
- [0032] 본 발명의 구조 및 조성물은 악성 종양과 같은 다양한 질환을 예방 또는 치료하는데 사용될 수 있다.
- [0033] 추가의 구현예에서, 본 발명은 본 발명의 하나 이상의 치료적 RNAi 분자의 전달 및 섭취를 위한 조성물 뿐 아니라 이의 사용 방법을 제공한다. 본 발명의 RNA-기반 조성물은 암과 같은 악성 종양을 예방 또는 치료하기 위한 방법에서 사용될 수 있다.
- [0034] 본 발명의 치료 조성물은 RNA 간섭에 활성인 핵산 분자를 포함한다. 치료 핵산 분자는 유전자 침묵화를 위해 GSTP1 (GST- π)에 표적될 수 있다.
- [0035] 다양한 구현예에서, 본 발명은 소형 간섭 RNA (siRNA)로서 활성일 수 있고, GST- π 유전자 발현을 조절 또는 침묵시킬 수 있는 다양한 분자를 제공한다.
- [0036] 본 발명의 siRNA는 악성 종양을 예방 또는 치료하기 위해 사용될 수 있다.
- [0037] 본 발명의 구현예는 추가로 악성 종양의 예방 또는 치료를 필요로 하는 대상체에 대한 본 발명의 siRNA의 전달을 위한 비히클, 제형, 또는 지지 나노입자 제형을 제공한다. 본 발명은 추가로 포유동물에게 치료제로서 siRNA를 투여하기 위한 방법을 고려한다.
- [0038] 본 발명의 치료 분자 및 조성물은 화합물 또는 조성물을 이를 필요로 하는 대상체에게 투여함으로써, GST- π 관련 질환을 예방 또는 치료하기 위해 RNA 간섭에 사용될 수 있다.
- [0039] 본 발명의 방법은 악성 종양을 예방 또는 치료하기 위해 본 발명의 화합물을 이용할 수 있다. 악성 종양은 다양한 질환, 예를 들어, GST- π 를 고도로 발현하는 암, 돌연변이된 KRAS를 발현하는 세포에 의해 야기된 암, 육종, 섬유육종, 악성 섬유 조직구종, 지방육종, 횡문근육종, 평활근육종, 혈관육종, 카포시 육종, 림프관육종, 활액막 육종, 연골육종, 골육종, 암종, 뇌종양, 두경부암, 유방암, 폐암, 식도암, 위암, 십이지장암, 결장직장암, 간암, 췌장암, 담낭암, 담관암, 신장암, 요도암, 방광암, 전립선암, 고환암, 자궁암, 난소암, 피부암, 백혈병, 악성 림프종, 상피성 악성 종양, 및 비-상피성 악성 종양에 존재할 수 있다.
- [0040] 특정 구현예에서, 본 발명의 치료 분자의 조합은 GST- π 유전자 발현의 침묵화 또는 억제에 사용될 수 있다.
- [0041] 본 발명은 다양한 RNAi 분자를 제공하며, 여기에서 각 분자는 폴리뉴클레오티드 센스 가닥 및 폴리뉴클레오티드 안티센스 가닥을 갖고; 분자의 각 가닥은 15 내지 30 개 뉴클레오티드 길이를 갖고; 안티센스 가닥의 15 내지 30 개 뉴클레오티드의 인접 영역 (contiguous region)은 GST- π 를 인코딩하는 mRNA의 서열에 상보적이고; 센스 가닥의 적어도 일부는 안티센스 가닥의 적어도 일부분에 상보적이고, 분자는 15 내지 30 개 뉴클레오티드 길이의 듀플렉스 영역을 갖는다.
- [0042] 본 발명의 RNAi 분자는 분자의 듀플렉스 영역에 위치하는, GST- π 를 인코딩하는 mRNA의 서열에 상보적인 안티센스 가닥의 15 내지 30 개 뉴클레오티드의 인접 영역을 가질 수 있다.
- [0043] 일부 구현예에서, RNAi 분자는 GST- π 를 인코딩하는 mRNA의 서열에 상보적인 안티센스 가닥의 15 내지 30 개 뉴클레오티드의 인접 영역을 가질 수 있다.
- [0044] 본 발명의 구현예는 또한 이를 필요로 하는 포유동물에서 악성 종양의 하나 이상의 증상의 예방, 치료 또는 완화, 또는 악성 종양을 발달시킬 위험의 감소, 또는 악성 종양의 개시의 지연을 위한 방법을 제공할 수 있다.
- [0045] GST- π 및 RNAi 분자
- [0046] 도 1은 GenBank 수탁 번호 NM_000852.3 (hGSTP1)에 기재되고, 986 개 뉴클레오티드 길이인 (SEQ ID NO: 1), 예시 표적 인간 글루타티온 S-트랜스페라아제 pi (인간 GST- π) mRNA의 핵산 서열을 나타낸다.
- [0047] 당업자는 보고된 서열이 시간의 흐름에 따라 변화할 수 있고 본원에서 핵산 분자에 필요한 임의의 변화를 그에 맞춰 포함할 수 있다는 것을 이해할 것이다.
- [0048] 본 발명의 구현예는 작은 핵산 분자를 사용하는 GST- π 발현의 유전자 침묵화를 위한 조성물 및 방법을 제공할 수 있다. 핵산 분자의 예는 RNA 간섭에서 활성인 분자 (RNAi 분자), 짧은 간섭하는 RNA (siRNA), 이중-가닥

RNA (dsRNA), 마이크로-RNA (miRNA), 및 짧은 헤어핀 RNA (shRNA) 분자, 뿐만 아니라 DNA-지향되는 RNA (ddRNA), Piwi-상호작용 RNA (piRNA), 및 리피트 (repeat) 연합된 siRNA (rasiRNA) 를 포함한다. 이러한 분자들은 GST- π 유전자 발현에 대한 RNA 간섭을 매개할 수 있다.

- [0049] 본원에서 개시된 조성물 및 방법은 또한 대상체에서 다양한 종류의 악성 종양을 치료하는데 사용될 수 있다.
- [0050] 본 발명의 핵산 분자 및 방법은 GST- π 를 인코딩하는 유전자의 발현을 하향 조절하는데 사용될 수 있다.
- [0051] 본 발명의 조성물 및 방법은 GST- π 단백질 및/또는 GST- π 단백질을 인코딩하는 유전자, GST- π 와 관련되는 질환, 병태 또는 장애, 예컨대 악성 종양의 유지 및/또는 발달과 관련되는 단백질을 및/또는 GST- π 를 인코딩하는 유전자의 발현을, 독립적으로 또는 조합으로, 조정 또는 조절할 수 있는 하나 이상의 핵산 분자를 포함할 수 있다.
- [0052] 본 발명의 조성물 및 방법은 GST- π 의 예시적인 서열과 관련하여 기재된다. 당업자는 본 발명의 다양한 양상 및 구현예가 임의의 관련된 GST- π 유전자, 서열, 또는 변이체, 예컨대 동족체 유전자 및 전사체 변이체, 및, 임의의 GST- π 유전자와 관련된 단일 뉴클레오타이드 다형성 (SNP) 을 포함하는, 다형성에 관한 것이라는 점을 이해할 것이다.
- [0053] 일부 구현예에서, 본 발명의 조성물 및 방법은 GST- π 유전자, 예를 들어 인간 GST- π 의 발현을 하향조절하는 이중-가닥 짧은 간섭하는 핵산 (siRNA) 분자를 제공할 수 있다.
- [0054] 본 발명의 RNAi 분자는 GST- π 및 임의의 상동성 서열을, 예를 들어, 상보적 서열을 사용하여 또는 추가의 표적 서열을 제공할 수 있는 비-표준적 (non-canonical) 염기쌍, 예를 들어, 미스매치 (mismatch) 및/또는 워블 (wobble) 염기쌍을 편입시킴으로써, 표적으로 삼을 수 있다.
- [0055] 미스매치가 확인되는 경우에, 비-표준적 염기쌍, 예를 들어, 미스매치 및/또는 워블 염기가 사용되어 하나 초과 유전자 서열을 표적으로 삼는 핵산 분자를 생성할 수 있다.
- [0056] 예를 들어, 비-표준적 염기쌍 예컨대 UU 및 CC 염기쌍이 사용되어 서열 상동성을 공유하는 상이한 GST- π 표적에 관한 서열을 표적화할 수 있는 핵산 분자를 생성할 수 있다. 따라서, RNAi 분자는 상동성 유전자 사이에 보존되어 있는 뉴클레오타이드 서열을 표적으로 삼을 수 있고, 단일 RNAi 분자가 사용되어 하나 초과 유전자의 발현을 억제할 수 있다.
- [0057] 일부 양상에서, 본 발명의 조성물 및 방법은 GST- π mRNA 에 대해 활성인 RNAi 분자를 포함하며, 여기에서 RNAi 분자는 GST- π 서열을 인코딩하는 임의의 mRNA 에 상보적인 서열을 포함한다.
- [0058] 일부 구현예에서, 본 공개의 RNAi 분자는 GST- π RNA 에 대한 활성을 가질 수 있으며, 여기에서 RNAi 분자는 변이체 GST- π 인코딩 서열을 갖는 RNA, 예를 들어, 악성 종양과 관련되는 것으로 당업계에 알려진 돌연변이체 GST- π 유전자에 상보적인 서열을 포함한다.
- [0059] 추가 구현예에서, 본 발명의 RNAi 분자는 GST- π 유전자의 뉴클레오타이드 서열과 상호작용하고 GST- π 유전자 발현의 침묵화를 매개할 수 있는 뉴클레오타이드 서열을 포함할 수 있다.
- [0060] GST- π mRNA 를 표적으로 삼는 본 발명의 RNAi 분자의 예가 표 1 및 2 에서 보여진다.

[0061]

표 1: GST- π 에 관한 RNAi 분자 서열

Ref Pos	SEQ ID NO	센스 가닥 (5'-->3') SEQ ID NOS:2 내지 608	SEQ ID NO	안티센스 가닥 (5'-->3') SEQ ID NOS:609 내지 1215
232	2	GCCGCAGUCUUCGCCACCAtt	609	UGGUGGCGAAGACUGCGGCgg
233	3	CCGCAGUCUUCGCCACCAUtt	610	AUGGUGGCGAAGACUGCGGcg
234	4	CGCAGUCUUCGCCACCAUGtt	611	CAUGGUGGCGAAGACUGCGgc
235	5	GCAGUCUUCGCCACCAUGCtt	612	GCAUGGUGGCGAAGACUGCgg
236	6	CAGUCUUCGCCACCAUGCCtt	613	GGCAUGGUGGCGAAGACUGcg
237	7	AGUCUUCGCCACCAUGCCGtt	614	CGGCAUGGUGGCGAAGACUgc
238	8	GUCUUCGCCACCAUGCCGCtt	615	GCGGCAUGGUGGCGAAGACTg
239	9	UCUUCGCCACCAUGCCGCCtt	616	GGCGGCAUGGUGGCGAAGAct
240	10	CUUCGCCACCAUGCCGCCtt	617	GGGCGGCAUGGUGGCGAAGAc
241	11	UUCGCCACCAUGCCGCCUtt	618	AGGGCGGCAUGGUGGCGAAGa
242	12	UCGCCACCAUGCCGCCUAtt	619	UAGGGCGGCAUGGUGGCGAag
243	13	CGCCACCAUGCCGCCUACtt	620	GUAGGGCGGCAUGGUGGCGaa
244	14	GCCACCAUGCCGCCUACAtt	621	UGUAGGGCGGCAUGGUGGCga
245	15	CCACCAUGCCGCCUACACtt	622	GUGUAGGGCGGCAUGGUGGcg
246	16	CACCAUGCCGCCUACACtt	623	GGUGUAGGGCGGCAUGGUGgc
247	17	ACCAUGCCGCCUACACGtt	624	CGGUGUAGGGCGGCAUGGUgg
248	18	CCAUGCCGCCUACACCGUtt	625	ACGGUGUAGGGCGGCAUGGtg
249	19	CAUGCCGCCUACACCGUGtt	626	CACGGUGUAGGGCGGCAUGgt
250	20	AUGCCGCCUACACCGUGGtt	627	CCACGGUGUAGGGCGGCAUgg
251	21	UGCCGCCUACACCGUGGUtt	628	ACCACGGUGUAGGGCGGCAtg
252	22	GCCGCCUACACCGUGGUtt	629	GACCACGGUGUAGGGCGGCat
253	23	CCGCCUACACCGUGGUCUtt	630	AGACCACGGUGUAGGGCGGca
254	24	CGCCUACACCGUGGUCUAtt	631	UAGACCACGGUGUAGGGCGgc
255	25	GCCUACACCGUGGUCUAUtt	632	AUAGACCACGGUGUAGGGCgg
256	26	CCCUACACCGUGGUCUAUUtt	633	AAUAGACCACGGUGUAGGGcg
257	27	CCUACACCGUGGUCUAUUUtt	634	AAAUAGACCACGGUGUAGGGgc
258	28	CUACACCGUGGUCUAUUUtt	635	GAAAUAGACCACGGUGUAGgg

[0062]

Ref Pos	SEQ ID NO	센스 가닥 (5'-->3') SEQ ID NOS:2 내지 608	SEQ ID NO	안티센스 가닥 (5'-->3') SEQ ID NOS:609 내지 1215
259	29	UACACCGUGGUCUAUUUCCttt	636	GGAAAUAGACCACGGUGUAgg
260	30	ACACCGUGGUCUAUUUCCttt	637	GGGAAAUAGACCACGGUGUag
261	31	CACCGUGGUCUAUUUCCCAttt	638	UGGGAAAUAGACCACGGUGta
262	32	ACCGUGGUCUAUUUCCAGttt	639	CUGGGAAAUAGACCACGGUgt
263	33	CCGUGGUCUAUUUCCAGUttt	640	ACUGGGAAAUAGACCACGGtg
264	34	CGUGGUCUAUUUCCAGUUttt	641	AACUGGGAAAUAGACCACGgt
265	35	GUGGUCUAUUUCCAGUUCttt	642	GAACUGGGAAAUAGACCACgg
266	36	UGGUCUAUUUCCAGUUCGttt	643	CGAACUGGGAAAUAGACCacg
267	37	GGUCUAUUUCCAGUUCGAtt	644	UCGAACUGGGAAAUAGACCac
268	38	GUCUAUUUCCAGUUCGAGttt	645	CUCGAACUGGGAAAUAGACca
269	39	UCUAUUUCCAGUUCGAGGttt	646	CCUCGAACUGGGAAAUAGAcc
270	40	CUAUUUCCAGUUCGAGGCttt	647	GCCUCGAACUGGGAAAUAGac
271	41	UAUUUCCAGUUCGAGGCCttt	648	GGCCUCGAACUGGGAAAUAg
272	42	AUUUCCAGUUCGAGGCCGttt	649	CGGCCUCGAACUGGGAAAUag
273	43	UUUCCAGUUCGAGGCCGttt	650	GCGGCCUCGAACUGGGAAAta
274	44	UUCCAGUUCGAGGCCGCUttt	651	AGCGGCCUCGAACUGGGAAat
275	45	UCCAGUUCGAGGCCGCGUttt	652	CAGCGGCCUCGAACUGGGAAa
276	46	CCCAGUUCGAGGCCGCGUttt	653	GCAGCGGCCUCGAACUGGGaa
277	47	CCAGUUCGAGGCCGCGUGttt	654	CGCAGCGGCCUCGAACUGGga
278	48	CAGUUCGAGGCCGCGUGCttt	655	GCGCAGCGGCCUCGAACUGgg
279	49	AGUUCGAGGCCGCGUGCGttt	656	CGCGCAGCGGCCUCGAACUgg
280	50	GUUCGAGGCCGCGUGCGGttt	657	CCGCGCAGCGGCCUCGAACtg
281	51	UUCGAGGCCGCGUGCGGGttt	658	GCCGCGCAGCGGCCUCGAAct
282	52	UCGAGGCCGCGUGCGGGCttt	659	GGCCGCGCAGCGGCCUCGAac
283	53	CGAGGCCGCGUGCGGGCCttt	660	GGCCGCGCAGCGGCCUCGaa
284	54	GAGGCCGCGUGCGGGCCUttt	661	AGGGCCGCGCAGCGGCCUCga
285	55	AGGCCGCGUGCGGGCCUGttt	662	CAGGGCCGCGCAGCGGCCUcg
286	56	GGCCGCGUGCGGGCCUGCttt	663	GCAGGGCCGCGCAGCGGCCctc

[0063]

Ref Pos	SEQ ID NO	센스 가닥 (5'-->3') SEQ ID NOS:2 내지 608	SEQ ID NO	안티센스 가닥 (5'-->3') SEQ ID NOS:609 내지 1215
287	57	GCCGCGCGCGGCCUGCGtt	664	CGCAGGGCCGCGCAGCGGcct
288	58	CCGCGCGCGGCCUGCGCtt	665	GCGCAGGGCCGCGCAGCGGcc
289	59	CGCGCGCGGCCUGCGCAtt	666	UGCGCAGGGCCGCGCAGCGgc
290	60	GCUGCGCGGCCUGCGCAUtt	667	AUGCGCAGGGCCGCGCAGCgg
291	61	CUGCGCGGCCUGCGCAUGtt	668	CAUGCGCAGGGCCGCGCAGcg
292	62	UGCGCGGCCUGCGCAUGCtt	669	GCAUGCGCAGGGCCGCGCAGc
293	63	GCGCGGCCUGCGCAUGCUtt	670	AGCAUGCGCAGGGCCGCGCag
294	64	CGCGGCCUGCGCAUGCUGtt	671	CAGCAUGCGCAGGGCCGCGca
295	65	GCGGCCUGCGCAUGCUGCtt	672	GCAGCAUGCGCAGGGCCGCGc
296	66	CGGCCUGCGCAUGCUGCUtt	673	AGCAGCAUGCGCAGGGCCGcg
297	67	GGCCUGCGCAUGCUGCUGtt	674	CAGCAGCAUGCGCAGGGCCgc
298	68	GCCUGCGCAUGCUGCUGGtt	675	CCAGCAGCAUGCGCAGGGCcg
299	69	CCUGCGCAUGCUGCUGGctt	676	GCCAGCAGCAUGCGCAGGGcc
300	70	CCUGCGCAUGCUGCUGGCAtt	677	UGCCAGCAGCAUGCGCAGGgc
301	71	CUGCGCAUGCUGCUGGCAGtt	678	CUGCCAGCAGCAUGCGCAGgg
302	72	UGCGCAUGCUGCUGGCAGAtt	679	UCUGCCAGCAGCAUGCGCagg
303	73	GCGCAUGCUGCUGGCAGAUtt	680	AUCUGCCAGCAGCAUGCGCag
304	74	CGCAUGCUGCUGGCAGAUctt	681	GAUCUGCCAGCAGCAUGCGca
305	75	GCAUGCUGCUGGCAGAUCAtt	682	UGAUCUGCCAGCAGCAUGCgc
306	76	CAUGCUGCUGGCAGAUCAgtt	683	CUGAUCUGCCAGCAGCAUGcg
307	77	AUGCUGCUGGCAGAUCAggtt	684	CCUGAUCUGCCAGCAGCAUgc
308	78	UGCUGCUGGCAGAUCAGGgtt	685	CCCUGAUCUGCCAGCAGCAtg
309	79	GCUGCUGGCAGAUCAGGGctt	686	GCCCUGAUCUGCCAGCAGCat
310	80	CUGCUGGCAGAUCAGGGCtt	687	GGCCCUGAUCUGCCAGCAGca
311	81	UGCUGGCAGAUCAGGGCCAtt	688	UGGCCUGAUCUGCCAGCAGc
312	82	GCUGGCAGAUCAGGGCCAGtt	689	CUGGCCUGAUCUGCCAGCag
313	83	CUGGCAGAUCAGGGCCAGAtt	690	UCUGGCCUGAUCUGCCAGca
314	84	UGGCAGAUCAGGGCCAGAGtt	691	CUCUGGCCUGAUCUGCCAGc

[0064]

Ref Pos	SEQ ID NO	센스 가닥 (5'-->3') SEQ ID NOS:2 내지 608	SEQ ID NO	안티센스 가닥 (5'-->3') SEQ ID NOS:609 내지 1215
315	85	GGCAGAUCAAGGCCAGAGCtt	692	GCUCUGGCCCUCAUCUGCCag
316	86	GCAGAUCAAGGCCAGAGCUtt	693	AGCUCUGGCCCUCAUCUGCca
317	87	CAGAUCAAGGCCAGAGCUGtt	694	CAGCUCUGGCCCUCAUCUGcc
318	88	AGAUCAGGCCAGAGCUGGtt	695	CCAGCUCUGGCCCUCAUCUgc
319	89	GAUCAGGCCAGAGCUGGAtt	696	UCCAGCUCUGGCCCUCAUCtg
320	90	AUCAGGCCAGAGCUGGAAtt	697	UCCAGCUCUGGCCCUCAUct
321	91	UCAGGCCAGAGCUGGAAGtt	698	CUUCCAGCUCUGGCCCUGAtc
322	92	CAGGCCAGAGCUGGAAGGtt	699	CCUCCAGCUCUGGCCCUGat
323	93	AGGCCAGAGCUGGAAGGAtt	700	UCCUCCAGCUCUGGCCCUga
324	94	GGGCCAGAGCUGGAAGGAGtt	701	CUCCUCCAGCUCUGGCCCtg
325	95	GGCCAGAGCUGGAAGGAGGtt	702	CCUCCUCCAGCUCUGGCCct
326	96	GCCAGAGCUGGAAGGAGGAtt	703	UCCUCCUCCAGCUCUGGCcc
327	97	CCAGAGCUGGAAGGAGGAGtt	704	CUCCUCCUCCAGCUCUGGcc
328	98	CAGAGCUGGAAGGAGGAGGtt	705	CCUCCUCCUCCAGCUCUGgc
329	99	AGAGCUGGAAGGAGGAGGUtt	706	ACCUCCUCCUCCAGCUCUgg
330	100	GAGCUGGAAGGAGGAGGUGtt	707	CACCUCCUCCUCCAGCUCtg
330	101	GAGCUGGAAGGAGGAGGUAAtt	708	UACCUCCUCCUCCAGCUCtg
331	102	AGCUGGAAGGAGGAGGUGGtt	709	CCACCUCCUCCUCCAGCUct
332	103	GCUGGAAGGAGGAGGUGGUtt	710	ACCACCUCCUCCUCCAGctc
333	104	CUGGAAGGAGGAGGUGGUGtt	711	CACCACCUCCUCCUCCAGct
334	105	UGGAAGGAGGAGGUGGUGAtt	712	UCACCACCUCCUCCUCCAgc
335	106	GGAAGGAGGAGGUGGUGACtt	713	GUCACCACCUCCUCCUCCag
336	107	GAAGGAGGAGGUGGUGACtt	714	GGUACCACCUCCUCCUCCca
337	108	AAGGAGGAGGUGGUGACCGtt	715	CGGUACCACCUCCUCCUcc
338	109	AGGAGGAGGUGGUGACCGUtt	716	ACGGUACCACCUCCUCCUtc
339	110	GGAGGAGGUGGUGACCGUGtt	717	CACGGUACCACCUCCUCCtt
340	111	GAGGAGGUGGUGACCGUGGtt	718	CCACGGUACCACCUCCUCct
341	112	AGGAGGUGGUGACCGUGGAtt	719	UCCACGGUACCACCUCCUcc

[0065]

Ref Pos	SEQ ID NO	센스 가닥 (5'-->3') SEQ ID NOS:2 내지 608	SEQ ID NO	안티센스 가닥 (5'-->3') SEQ ID NOS:609 내지 1215
342	113	GGAGGUGGUGACCGUGGAGtt	720	CUCCACGGUCACCACCUCctc
343	114	GAGGUGGUGACCGUGGAGAtt	721	UCUCCACGGUCACCACCUCct
344	115	AGGUGGUGACCGUGGAGActt	722	GUCUCCACGGUCACCACCUCc
345	116	GGUGGUGACCGUGGAGACGtt	723	CGUCUCCACGGUCACCACCtc
346	117	GUGGUGACCGUGGAGACGUtt	724	ACGUCUCCACGGUCACCACct
347	118	UGGUGACCGUGGAGACGUGtt	725	CACGUCUCCACGGUCACCAcc
348	119	GGUGACCGUGGAGACGUGGtt	726	CCACGUCUCCACGGUCACCac
349	120	GUGACCGUGGAGACGUGGCtt	727	GCCACGUCUCCACGGUCACca
350	121	UGACCGUGGAGACGUGGCAtt	728	UGCCACGUCUCCACGGUCAcc
351	122	GACCGUGGAGACGUGGCAGtt	729	CUGCCACGUCUCCACGGUCac
352	123	ACCGUGGAGACGUGGCAGGtt	730	CCUGCCACGUCUCCACGGUca
353	124	CCGUGGAGACGUGGCAGGAtt	731	UCCUGCCACGUCUCCACGGtc
354	125	CGUGGAGACGUGGCAGGAGtt	732	CUCCUGCCACGUCUCCACGgt
355	126	GUGGAGACGUGGCAGGAGGtt	733	CCUCCUGCCACGUCUCCACgg
356	127	UGGAGACGUGGCAGGAGGGtt	734	CCUCCUGCCACGUCUCCAcg
357	128	GGAGACGUGGCAGGAGGGCtt	735	GCCUCCUGCCACGUCUCCac
358	129	GAGACGUGGCAGGAGGGCUtt	736	AGCCUCCUGCCACGUCUCca
359	130	AGACGUGGCAGGAGGGCUCtt	737	GAGCCUCCUGCCACGUCUcc
360	131	GACGUGGCAGGAGGGCUCAtt	738	UGAGCCUCCUGCCACGUctc
361	132	ACGUGGCAGGAGGGCUCActt	739	GUGAGCCUCCUGCCACGUct
362	133	CGUGGCAGGAGGGCUCACUtt	740	AGUGAGCCUCCUGCCACGtc
363	134	GUGGCAGGAGGGCUCACUCtt	741	GAGUGAGCCUCCUGCCACgt
364	135	UGGCAGGAGGGCUCACUCAtt	742	UGAGUGAGCCUCCUGCCAcg
365	136	GGCAGGAGGGCUCACUCAAtt	743	UUGAGUGAGCCUCCUGCCac
366	137	GCAGGAGGGCUCACUCAAAtt	744	UUUGAGUGAGCCUCCUGCca
367	138	CAGGAGGGCUCACUCAAAGtt	745	CUUUGAGUGAGCCUCCUGcc
368	139	AGGAGGGCUCACUCAAAGCtt	746	GCUUUGAGUGAGCCUCCUgc
369	140	GGAGGGCUCACUCAAAGCCtt	747	GGCUUUGAGUGAGCCUCCtg

[0066]

Ref Pos	SEQ ID NO	센스 가닥 (5'-->3') SEQ ID NOS:2 내지 608	SEQ ID NO	안티센스 가닥 (5'-->3') SEQ ID NOS:609 내지 1215
370	141	GAGGGCUCACUCAAAGCCUtt	748	AGGCUUUGAGUGAGCCCUct
371	142	AGGGCUCACUCAAAGCCUctt	749	GAGGCUUUGAGUGAGCCCUcc
372	143	GGGCUCACUCAAAGCCUCCtt	750	GGAGGCUUUGAGUGAGCCctc
373	144	GGCUCACUCAAAGCCUCCUtt	751	AGGAGGCUUUGAGUGAGCCct
374	145	GCUCACUCAAAGCCUCCUGtt	752	CAGGAGGCUUUGAGUGAGcc
375	146	CUCACUCAAAGCCUCCUGCtt	753	GCAGGAGGCUUUGAGUGAGcc
376	147	UCACUCAAAGCCUCCUGCCtt	754	GGCAGGAGGCUUUGAGUGAgc
377	148	CACUCAAAGCCUCCUGCCUtt	755	AGGCAGGAGGCUUUGAGUGag
378	149	ACUCAAAGCCUCCUGCCUAtt	756	UAGGCAGGAGGCUUUGAGUga
379	150	CUCAAAGCCUCCUGCCUAUtt	757	AUAGGCAGGAGGCUUUGAGtg
380	151	UCAAAGCCUCCUGCCUAUAtt	758	UAUAGGCAGGAGGCUUUGAg
381	152	CAAAGCCUCCUGCCUAUACtt	759	GUUAAGGCAGGAGGCUUUGag
382	153	AAAGCCUCCUGCCUAUACGtt	760	CGUAUAGGCAGGAGGCUUga
383	154	AAGCCUCCUGCCUAUACGGtt	761	CCGUUAAGGCAGGAGGCUUtg
384	155	AGCCUCCUGCCUAUACGGGtt	762	CCCGUAUAGGCAGGAGGCUtt
385	156	GCCUCCUGCCUAUACGGGCtt	763	GCCCGUAUAGGCAGGAGGctt
386	157	CCUCCUGCCUAUACGGGCAtt	764	UGCCCGUAUAGGCAGGAGGct
387	158	CUCCUGCCUAUACGGGCAGtt	765	CUGCCCGUAUAGGCAGGAGgc
388	159	UCCUGCCUAUACGGGCAGCtt	766	GCUGCCCGUAUAGGCAGGAgg
389	160	CCUGCCUAUACGGGCAGCUtt	767	AGCUGCCCGUAUAGGCAGGag
390	161	CUGCCUAUACGGGCAGCUCtt	768	GAGCUGCCCGUAUAGGCAGga
391	162	UGCCUAUACGGGCAGCUCCtt	769	GGAGCUGCCCGUAUAGGCAGg
392	163	GCCUAUACGGGCAGCUCCctt	770	GGGAGCUGCCCGUAUAGGCag
409	164	CCCAAGUCCAGGACGGAGtt	771	CUCCGUCCUGGAACUUGGGga
410	165	CCAAGUCCAGGACGGAGAtt	772	UCUCCGUCCUGGAACUUGGgg
411	166	CAAGUCCAGGACGGAGACtt	773	GUCUCCGUCCUGGAACUUGgg
412	167	AAGUCCAGGACGGAGACCtt	774	GGUCUCCGUCCUGGAACUUGg
413	168	AGUCCAGGACGGAGACCUtt	775	AGGUCUCCGUCCUGGAACUtg

[0067]

Ref Pos	SEQ ID NO	센스 가닥 (5'-->3') SEQ ID NOS:2 내지 608	SEQ ID NO	안티센스 가닥 (5'-->3') SEQ ID NOS:609 내지 1215
414	169	GUUCCAGGACGGAGACCUCttt	776	GAGGUCUCCGUCCUGGAACttt
415	170	UUCCAGGACGGAGACCUCAttt	777	UGAGGUCUCCGUCCUGGAActt
416	171	UCCAGGACGGAGACCUCACttt	778	GUGAGGUCUCCGUCCUGGAac
417	172	CCAGGACGGAGACCUCACctt	779	GGUGAGGUCUCCGUCCUGGaa
418	173	CAGGACGGAGACCUCACCCttt	780	GGGUGAGGUCUCCGUCCUGga
419	174	AGGACGGAGACCUCACCCUttt	781	AGGGUGAGGUCUCCGUCCUgg
420	175	GGACGGAGACCUCACCCUGttt	782	CAGGGUGAGGUCUCCGUCCtg
421	176	GACGGAGACCUCACCCUGUttt	783	ACAGGGUGAGGUCUCCGUCCt
422	177	ACGGAGACCUCACCCUGUAttt	784	UACAGGGUGAGGUCUCCGUcc
423	178	CGGAGACCUCACCCUGUACttt	785	GUACAGGGUGAGGUCUCCGtc
424	179	GGAGACCUCACCCUGUACctt	786	GGUACAGGGUGAGGUCUCCgt
425	180	GAGACCUCACCCUGUACCAttt	787	UGGUACAGGGUGAGGUCUccg
426	181	AGACCUCACCCUGUACCAgttt	788	CUGGUACAGGGUGAGGUCUcc
427	182	GACCUCACCCUGUACCAgu	789	ACUGGUACAGGGUGAGGUctc
428	183	ACCUCACCCUGUACCAGUctt	790	GACUGGUACAGGGUGAGGUct
429	184	CCUCACCCUGUACCAGUCCttt	791	GGACUGGUACAGGGUGAGGtc
430	185	CUCACCCUGUACCAGUCCAttt	792	UGGACUGGUACAGGGUGAGgt
431	186	UCACCCUGUACCAGUCCAAtt	793	UUGGACUGGUACAGGGUGAgg
432	187	CACCCUGUACCAGUCCAUA	794	AUUGGACUGGUACAGGGUGag
433	188	ACCCUGUACCAGUCCAUAAtt	795	UAUUGGACUGGUACAGGGUGa
434	189	CCCUGUACCAGUCCAUAUctt	796	GUAUUGGACUGGUACAGGGtg
435	190	CCUGUACCAGUCCAUAUCCttt	797	GGUAUUGGACUGGUACAGGgt
436	191	CUGUACCAGUCCAUAUACAtt	798	UGGUAUUGGACUGGUACAGgg
437	192	UGUACCAGUCCAUAUACCAUttt	799	AUGGUAUUGGACUGGUACAgg
438	193	GUACCAGUCCAUAUACCAUctt	800	GAUGGUAUUGGACUGGUACag
439	194	UACCAGUCCAUAUACCAUCCttt	801	GGAUGGUAUUGGACUGGUACA
440	195	ACCAGUCCAUAUACCAUCCUttt	802	AGGAUGGUAUUGGACUGGUac
441	196	CCAGUCCAUAUACCAUCCUGttt	803	CAGGAUGGUAUUGGACUGGta

[0068]

Ref Pos	SEQ ID NO	센스 가닥 (5'-->3') SEQ ID NOS:2 내지 608	SEQ ID NO	안티센스 가닥 (5'-->3') SEQ ID NOS:609 내지 1215
442	197	CAGUCCAAUACCAUCCUGCttt	804	GCAGGAUGGUAAUUGGACUGgt
443	198	AGUCCAAUACCAUCCUGCGttt	805	CGCAGGAUGGUAAUUGGACUgg
444	199	GUCCAAUACCAUCCUGCGUttt	806	ACGCAGGAUGGUAAUUGGACtg
445	200	UCCAAUACCAUCCUGCGUCttt	807	GACGCAGGAUGGUAAUUGGAct
446	201	CCAAUACCAUCCUGCGUCAttt	808	UGACGCAGGAUGGUAAUUGGac
447	202	CAAUACCAUCCUGCGUCActtt	809	GUGACGCAGGAUGGUAAUUGga
448	203	AAUACCAUCCUGCGUCACttt	810	GGUGACGCAGGAUGGUAAUugg
449	204	AUACCAUCCUGCGUCACUttt	811	AGGUGACGCAGGAUGGUAAutg
450	205	UACCAUCCUGCGUCACCUGttt	812	CAGGUGACGCAGGAUGGUAtt
451	206	ACCAUCCUGCGUCACCUGGttt	813	CCAGGUGACGCAGGAUGGUat
452	207	CCAUCCUGCGUCACCUGGGttt	814	CCCAGGUGACGCAGGAUGGta
453	208	CAUCCUGCGUCACCUGGGCttt	815	GCCCAGGUGACGCAGGAUGgt
454	209	AUCCUGCGUCACCUGGGCCttt	816	GGCCCAGGUGACGCAGGAUgg
455	210	UCCUGCGUCACCUGGGCCGttt	817	CGGCCAGGUGACGCAGGAtg
456	211	CCUGCGUCACCUGGGCCGctt	818	GCGGCCAGGUGACGCAGGat
457	212	CUGCGUCACCUGGGCCGCAtt	819	UGCGGCCAGGUGACGCAGga
458	213	UGCGUCACCUGGGCCGCActt	820	GUGCGGCCAGGUGACGCAGg
459	214	GCGUCACCUGGGCCGCACctt	821	GGUGCGGCCAGGUGACGCag
460	215	CGUCACCUGGGCCGCACCCttt	822	GGGUGCGGCCAGGUGACGca
461	216	GUCACCUGGGCCGCACCCUttt	823	AGGGUGCGGCCAGGUGACgc
462	217	UCACCUGGGCCGCACCCUttt	824	AAGGGUGCGGCCAGGUGAcg
463	218	CACCUGGGCCGCACCCUUGttt	825	CAAGGGUGCGGCCAGGUGac
464	219	ACCUGGGCCGCACCCUUGGttt	826	CCAAGGGUGCGGCCAGGUga
465	220	CCUGGGCCGCACCCUUGGttt	827	CCAAGGGUGCGGCCAGGtg
466	221	CUGGGCCGCACCCUUGGGCttt	828	GCCAAGGGUGCGGCCAGgt
467	222	UGGGCCGCACCCUUGGGCUttt	829	AGCCAAGGGUGCGGCCAgg
468	223	GGGCCGCACCCUUGGGCUCttt	830	GAGCCAAGGGUGCGGCCag
469	224	GGCCGCACCCUUGGGCUCUttt	831	AGAGCCAAGGGUGCGGCCca

[0069]

Ref Pos	SEQ ID NO	센스 가닥 (5'-->3') SEQ ID NOS:2 내지 608	SEQ ID NO	안티센스 가닥 (5'-->3') SEQ ID NOS:609 내지 1215
470	225	GCCGCACCCUUGGGCUCUAAtt	832	UAGAGCCCAAGGGUGCGGCcc
471	226	CCGCACCCUUGGGCUCUAUtt	833	AUAGAGCCCAAGGGUGCGGcc
472	227	CGCACCCUUGGGCUCUAUGtt	834	CAUAGAGCCCAAGGGUGCGgc
473	228	GCACCCUUGGGCUCUAUGGtt	835	CCAUAGAGCCCAAGGGUGCgg
474	229	CACCCUUGGGCUCUAUGGtt	836	CCCAUAGAGCCCAAGGGUGcg
475	230	ACCCUUGGGCUCUAUGGGAtt	837	UCCCAUAGAGCCCAAGGGUgc
476	231	CCCUUGGGCUCUAUGGGAAtt	838	UUCCCAUAGAGCCCAAGGGtg
477	232	CCUUGGGCUCUAUGGGAAGtt	839	CUUCCCAUAGAGCCCAAGGgt
478	233	CUUGGGCUCUAUGGGAAGGtt	840	CCUCCCAUAGAGCCCAAGgg
479	234	UUGGGCUCUAUGGGAAGGAtt	841	UCCUCCCAUAGAGCCCAAgg
480	235	UGGGCUCUAUGGGAAGGACtt	842	GUCCUCCCAUAGAGCCCAag
481	236	GGGCUCUAUGGGAAGGACtt	843	GGUCCUCCCAUAGAGCCCAa
482	237	GGCUCUAUGGGAAGGACAtt	844	UGGUCCUCCCAUAGAGCCca
483	238	GCUCUAUGGGAAGGACCAGtt	845	CUGGUCCUCCCAUAGAGCcc
484	239	CUCUAUGGGAAGGACCAGCtt	846	GCUGGUCCUCCCAUAGAGcc
485	240	UCUAUGGGAAGGACCAGCAtt	847	UGCUGGUCCUCCCAUAGAgc
486	241	CUAUGGGAAGGACCAGCAGtt	848	CUGCUGGUCCUCCCAUAGag
487	242	UAUGGGAAGGACCAGCAGGtt	849	CCUGCUGGUCCUCCCAUAga
488	243	AUGGGAAGGACCAGCAGGAtt	850	UCCUGCUGGUCCUCCCAUag
489	244	UGGGAAGGACCAGCAGGAGtt	851	CUCCUGCUGGUCCUCCCAta
490	245	GGGAAGGACCAGCAGGAGGtt	852	CCUCCUGCUGGUCCUCCCat
491	246	GGAAGGACCAGCAGGAGGCtt	853	GCCUCCUGCUGGUCCUCCca
492	247	GAAGGACCAGCAGGAGGCAtt	854	UGCCUCCUGCUGGUCCUUCcc
493	248	AAGGACCAGCAGGAGGCAGtt	855	CUGCCUCCUGCUGGUCCUcc
494	249	AGGACCAGCAGGAGGCAGCtt	856	GCUGCCUCCUGCUGGUCCUtc
495	250	GGACCAGCAGGAGGCAGCCtt	857	GGCUGCCUCCUGCUGGUCCtt
496	251	GACCAGCAGGAGGCAGCCtt	858	GGGCUGCCUCCUGCUGGUCCt
497	252	ACCAGCAGGAGGCAGCCUtt	859	AGGGCUGCCUCCUGCUGGUcc

[0070]

Ref Pos	SEQ ID NO	센스 가닥 (5'-->3') SEQ ID NOS:2 내지 608	SEQ ID NO	안티센스 가닥 (5'-->3') SEQ ID NOS:609 내지 1215
498	253	CCAGCAGGAGGCAGCCCUGttt	860	CAGGGCUGCCUCCUGCUGGtc
499	254	CAGCAGGAGGCAGCCCUGGttt	861	CCAGGGCUGCCUCCUGCUGgt
500	255	AGCAGGAGGCAGCCCUGGUttt	862	ACCAGGGCUGCCUCCUGCUgg
501	256	GCAGGAGGCAGCCCUGGUGttt	863	CACCAGGGCUGCCUCCUGCtg
502	257	CAGGAGGCAGCCCUGGUGGttt	864	CCACCAGGGCUGCCUCCUGct
503	258	AGGAGGCAGCCCUGGUGGAtt	865	UCCACCAGGGCUGCCUCCUgc
504	259	GGAGGCAGCCCUGGUGGACttt	866	GUCCACCAGGGCUGCCUCCtg
505	260	GAGGCAGCCCUGGUGGACAtt	867	UGUCCACCAGGGCUGCCUCct
506	261	AGGCAGCCCUGGUGGACAUttt	868	AUGUCCACCAGGGCUGCCUcc
507	262	GGCAGCCCUGGUGGACAUGttt	869	CAUGUCCACCAGGGCUGCCtc
508	263	GCAGCCCUGGUGGACAUGGttt	870	CCAUGUCCACCAGGGCUGCct
509	264	CAGCCCUGGUGGACAUGGUttt	871	ACCAUGUCCACCAGGGCUGcc
510	265	AGCCCUGGUGGACAUGGUGttt	872	CACCAUGUCCACCAGGGCUgc
511	266	GCCCUGGUGGACAUGGUGAtt	873	UCACCAUGUCCACCAGGGCtg
512	267	CCCUGGUGGACAUGGUGAAttt	874	UUCACCAUGUCCACCAGGGct
513	268	CCUGGUGGACAUGGUGAAUttt	875	AUUCACCAUGUCCACCAGGgc
514	269	CUGGUGGACAUGGUGAAUGttt	876	CAUUCACCAUGUCCACCAGgg
515	270	UGGUGGACAUGGUGAAUGAtt	877	UCAUUCACCAUGUCCACAgg
516	271	GGUGGACAUGGUGAAUGACttt	878	GUCAUUCACCAUGUCCACCag
517	272	GUGGACAUGGUGAAUGACGttt	879	CGUCAUUCACCAUGUCCACca
518	273	UGGACAUGGUGAAUGACGGttt	880	CCGUCAUUCACCAUGUCCAcc
519	274	GGACAUGGUGAAUGACGGCttt	881	GCCGUCAUUCACCAUGUCCac
520	275	GACAUGGUGAAUGACGGCGttt	882	CGCCGUCAUUCACCAUGUCca
521	276	ACAUGGUGAAUGACGGCGUttt	883	ACGCCGUCAUUCACCAUGUcc
522	277	CAUGGUGAAUGACGGCGUGttt	884	CACGCCGUCAUUCACCAUGtc
523	278	AUGGUGAAUGACGGCGUGGttt	885	CCACGCCGUCAUUCACCAUgt
524	279	UGGUGAAUGACGGCGUGGAtt	886	UCCACGCCGUCAUUCACCAtg
525	280	GGUGAAUGACGGCGUGGAGttt	887	CUCCACGCCGUCAUUCACCat

[0071]

Ref Pos	SEQ ID NO	센스 가닥 (5'-->3') SEQ ID NOS:2 내지 608	SEQ ID NO	안티센스 가닥 (5'-->3') SEQ ID NOS:609 내지 1215
526	281	GUGAAUGACGGCGUGGAGGttt	888	CCUCCACGCCGUGCAUUCACca
527	282	UGAAUGACGGCGUGGAGGAttt	889	UCCUCCACGCCGUGCAUUCAcc
528	283	GAAUGACGGCGUGGAGGACttt	890	GUCCUCCACGCCGUGCAUUCac
529	284	AAUGACGGCGUGGAGGACttt	891	GGUCCUCCACGCCGUGCAUuca
530	285	AUGACGGCGUGGAGGACCUttt	892	AGGUCCUCCACGCCGUGCAUtc
531	286	UGACGGCGUGGAGGACCUCttt	893	GAGGUCCUCCACGCCGUCAtt
532	287	GACGGCGUGGAGGACCUCttt	894	GGAGGUCCUCCACGCCGUCat
533	288	ACGGCGUGGAGGACCUCGttt	895	CGGAGGUCCUCCACGCCGUca
534	289	CGGCGUGGAGGACCUCGctt	896	GCGGAGGUCCUCCACGCCGtc
535	290	GGCGUGGAGGACCUCGCUttt	897	AGCGGAGGUCCUCCACGCCgt
536	291	GCGUGGAGGACCUCGCUgtt	898	CAGCGGAGGUCCUCCACGCcg
537	292	CGUGGAGGACCUCGCUgtt	899	GCAGCGGAGGUCCUCCACGcc
538	293	GUGGAGGACCUCGCUGCAttt	900	UGCAGCGGAGGUCCUCCACgc
539	294	UGGAGGACCUCGCUGCAAtt	901	UUGCAGCGGAGGUCCUCCAcg
540	295	GGAGGACCUCGCUGCAAAttt	902	UUUGCAGCGGAGGUCCUCCac
541	296	GAGGACCUCGCUGCAAAUttt	903	AUUUGCAGCGGAGGUCCUCca
542	297	AGGACCUCGCUGCAAAUAtt	904	UAUUUGCAGCGGAGGUCCUcc
543	298	GGACCUCGCUGCAAAUACttt	905	GUAUUUGCAGCGGAGGUCCtc
544	299	GACCUCGCUGCAAAUACAtt	906	UGUAUUUGCAGCGGAGGUcct
545	300	ACCUCGCUGCAAAUACAUttt	907	AUGUAUUUGCAGCGGAGGUcc
546	301	CCUCGCUGCAAAUACAUCttt	908	GAUGUAUUUGCAGCGGAGGtc
547	302	CUCCGCUGCAAAUACAUCUttt	909	AGAUGUAUUUGCAGCGGAGgt
548	303	UCCGCUGCAAAUACAUCUCttt	910	GAGAUGUAUUUGCAGCGGAgg
549	304	CCGCUGCAAAUACAUCUCttt	911	GGAGAUGUAUUUGCAGCGGag
550	305	CGCUGCAAAUACAUCUCCttt	912	GGGAGAUGUAUUUGCAGCGga
551	306	GCUGCAAAUACAUCUCCUttt	913	AGGGAGAUGUAUUUGCAGCgg
552	307	CUGCAAAUACAUCUCCUCttt	914	GAGGGAGAUGUAUUUGCAGcg
553	308	UGCAAAUACAUCUCCUCAttt	915	UGAGGGAGAUGUAUUUGCAGc

[0072]

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554	309	GCAAUACAUCUCCCUCAUtt	916	AUGAGGGAGAUGUAUUUGCag
555	310	CAAAUACAUCUCCCUCAUCtt	917	GAUGAGGGAGAUGUAUUUGca
556	311	AAAUACAUCUCCCUCAUCUtt	918	AGAUGAGGGAGAUGUAUUUgc
557	312	AAUACAUCUCCCUCAUCUAtt	919	UAGAUGAGGGAGAUGUAUUtg
558	313	AUACAUCUCCCUCAUCUActt	920	GUAGAUGAGGGAGAUGUAUtt
559	314	UACAUCUCCCUCAUCUACAtt	921	UGUAGAUGAGGGAGAUGUAAtt
560	315	ACAUCUCCCUCAUCUACACtt	922	GUGUAGAUGAGGGAGAUGUat
561	316	CAUCUCCCUCAUCUACACtt	923	GGUGUAGAUGAGGGAGAUGta
562	317	AUCUCCCUCAUCUACACCAtt	924	UGGUGUAGAUGAGGGAGUgt
563	318	UCUCCCUCAUCUACACCAAtt	925	UUGGUGUAGAUGAGGGAGAtg
563	319	GCUCCCUCAUCUACACCAAtt	926	UUGGUGUAGAUGAGGGAGCtg
564	320	CUCCCUCAUCUACACCAACTt	927	GUUGGUGUAGAUGAGGGAGat
565	321	UCCCUCAUCUACACCAACUtt	928	AGUUGGUGUAGAUGAGGGAGa
565	322	CUCCCUCAUCUACACCAAAtt	929	UUUGGUGUAGAUGAGGGAGat
566	323	CCCUCAUCUACACCAACUAtt	930	UAGUUGGUGUAGAUGAGGGag
567	324	CCUCAUCUACACCAACUAUtt	931	AUAGUUGGUGUAGAUGAGGga
567	325	CCUCAUCUACACCAACUAAtt	932	UUAGUUGGUGUAGAUGAGGga
568	326	CUCAUCUACACCAACUAUGtt	933	CAUAGUUGGUGUAGAUGAGgg
569	327	UCAUCUACACCAACUAUGAtt	934	UCAUAGUUGGUGUAGAUGAgg
570	328	CAUCUACACCAACUAUGAGtt	935	CUCAUAGUUGGUGUAGAUGag
571	329	AUCUACACCAACUAUGAGGtt	936	CCUCAUAGUUGGUGUAGUga
572	330	UCUACACCAACUAUGAGGctt	937	GCCUCAUAGUUGGUGUAGAtg
573	331	CUACACCAACUAUGAGGCGtt	938	CGCCUCAUAGUUGGUGUAGat
574	332	UACACCAACUAUGAGGCGGtt	939	CCGCCUCAUAGUUGGUGUAg
575	333	ACACCAACUAUGAGGCGGGtt	940	CCCGCCUCAUAGUUGGUGUag
576	334	CACCAACUAUGAGGCGGGctt	941	GCCCGCCUCAUAGUUGGUGta
577	335	ACCAACUAUGAGGCGGGCAtt	942	UGCCCGCCUCAUAGUUGGUgt
578	336	CCAACUAUGAGGCGGGCAAtt	943	UUGCCCGCCUCAUAGUUGGtg

[0073]

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579	337	CAACUAUGAGGCGGGCAAGtt	944	CUUGCCCCGCCUCAUAGUUGgt
580	338	AACUAUGAGGCGGGCAAGGtt	945	CCUUGCCCCGCCUCAUAGUUGg
581	339	ACUAUGAGGCGGGCAAGGAtt	946	UCCUUGCCCCGCCUCAUAGUtg
582	340	CUAUGAGGCGGGCAAGGAUtt	947	AUCCUUGCCCCGCCUCAUAGtt
583	341	UAUGAGGCGGGCAAGGAUGtt	948	CAUCCUUGCCCCGCCUCAUAgt
584	342	AUGAGGCGGGCAAGGAUGAtt	949	UCAUCCUUGCCCCGCCUCAUag
585	343	UGAGGCGGGCAAGGAUGActt	950	GUCAUCCUUGCCCCGCCUCAta
586	344	GAGGCGGGCAAGGAUGACUtt	951	AGUCAUCCUUGCCCCGCCUCAat
587	345	AGGCGGGCAAGGAUGACUAAtt	952	UAGUCAUCCUUGCCCCGCCUCAca
588	346	GGCGGGCAAGGAUGACUAUtt	953	AUAGUCAUCCUUGCCCCGCCUct
589	347	GCGGGCAAGGAUGACUAUGtt	954	CAUAGUCAUCCUUGCCCCGCCct
590	348	CGGGCAAGGAUGACUAUGUtt	955	ACAUAGUCAUCCUUGCCCCGCCc
591	349	GGGCAAGGAUGACUAUGUGtt	956	CACAUAGUCAUCCUUGCCCCGgc
592	350	GGCAAGGAUGACUAUGUGAtt	957	UCACAUAGUCAUCCUUGCCCgc
593	351	GCAAGGAUGACUAUGUGAAtt	958	UUCACAUAGUCAUCCUUGCCc
594	352	CAAGGAUGACUAUGUGAAGtt	959	CUUCACAUAGUCAUCCUUGcc
595	353	AAGGAUGACUAUGUGAAGGtt	960	CCUUCACAUAGUCAUCCUUGc
596	354	AGGAUGACUAUGUGAAGGctt	961	GCCUUCACAUAGUCAUCCUtg
597	355	GGAUGACUAUGUGAAGGCAtt	962	UGCCUUCACAUAGUCAUCCtt
598	356	GAUGACUAUGUGAAGGCActt	963	GUGCCUUCACAUAGUCAUCct
599	357	AUGACUAUGUGAAGGCACUtt	964	AGUGCCUUCACAUAGUCAUcc
600	358	UGACUAUGUGAAGGCACUGtt	965	CAGUGCCUUCACAUAGUCAtc
601	359	GACUAUGUGAAGGCACUGCtt	966	GCAGUGCCUUCACAUAGUCAat
602	360	ACUAUGUGAAGGCACUGCCtt	967	GGCAGUGCCUUCACAUAGUca
603	361	CUAUGUGAAGGCACUGCCCtt	968	GGGCAGUGCCUUCACAUAGtc
604	362	UAUGUGAAGGCACUGCCCGtt	969	CGGGCAGUGCCUUCACAUAg
605	363	AUGUGAAGGCACUGCCCGGtt	970	CCGGGCAGUGCCUUCACAUag
606	364	UGUGAAGGCACUGCCCGGGtt	971	CCCGGCAGUGCCUUCACAta

[0074]

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607	365	GUGAAGGCACUGCCCGGGCttt	972	GCCCCGGGCAGUGCCUUCACat
608	366	UGAAGGCACUGCCCGGGCAttt	973	UGCCCCGGGCAGUGCCUUCaCa
609	367	GAAGGCACUGCCCGGGCAAtt	974	UUGCCCCGGGCAGUGCCUUCac
610	368	AAGGCACUGCCCGGGCAACttt	975	GUUGCCCCGGGCAGUGCCUuca
611	369	AGGCACUGCCCGGGCAACUttt	976	AGUUGCCCCGGGCAGUGCCUtc
612	370	GGCACUGCCCGGGCAACUGttt	977	CAGUUGCCCCGGGCAGUGCCttt
613	371	GCACUGCCCGGGCAACUGAtt	978	UCAGUUGCCCCGGGCAGUGCct
614	372	CACUGCCCGGGCAACUGAAttt	979	UUCAGUUGCCCCGGGCAGUGcc
615	373	ACUGCCCGGGCAACUGAAGttt	980	CUUCAGUUGCCCCGGGCAGUgc
616	374	CUGCCCGGGCAACUGAAGCttt	981	GCUUCAGUUGCCCCGGGCAGtg
617	375	UGCCCGGGCAACUGAAGCCttt	982	GGCUUCAGUUGCCCCGGGCagt
618	376	GCCCGGGCAACUGAAGCCUttt	983	AGGCUUCAGUUGCCCCGGGCag
619	377	CCCGGGCAACUGAAGCCUUttt	984	AAGGCUUCAGUUGCCCCGGGca
620	378	CCGGGCAACUGAAGCCUUUttt	985	AAAGGCUUCAGUUGCCCCGGgc
621	379	CGGGCAACUGAAGCCUUUUttt	986	AAAAGGCUUCAGUUGCCCCGgg
622	380	GGGCAACUGAAGCCUUUUGttt	987	CAAAAGGCUUCAGUUGCCCCgg
623	381	GGCAACUGAAGCCUUUUGAtt	988	UCAAAGGCUUCAGUUGCCcg
624	382	GCAACUGAAGCCUUUUGAGttt	989	CUCAAAGGCUUCAGUUGCcc
625	383	CAACUGAAGCCUUUUGAGAtt	990	UCUCAAAGGCUUCAGUUGcc
626	384	AACUGAAGCCUUUUGAGACttt	991	GUCUCAAAGGCUUCAGUugc
627	385	ACUGAAGCCUUUUGAGACttt	992	GGUCUCAAAGGCUUCAGUtg
627	386	ACUGAAGCCUUUUGAGACAtt	993	UGUCUCAAAGGCUUCAGUtg
628	387	CUGAAGCCUUUUGAGACCCttt	994	GGGUCUCAAAGGCUUCAGttt
629	388	UGAAGCCUUUUGAGACCCUttt	995	AGGGUCUCAAAGGCUUCAgt
630	389	GAAGCCUUUUGAGACCCUGttt	996	CAGGGUCUCAAAGGCUUCag
631	390	AAGCCUUUUGAGACCCUGttt	997	GCAGGGUCUCAAAGGCUuca
631	391	GAAGCCUUUUGAGACCCUAtt	998	UAGGGUCUCAAAGGCUUCag
632	392	AGCCUUUUGAGACCCUGCttt	999	AGCAGGGUCUCAAAGGCUtc

[0075]

Ref Pos	SEQ ID NO	센스 가닥 (5'-->3') SEQ ID NOS:2 내지 608	SEQ ID NO	안티센스 가닥 (5'-->3') SEQ ID NOS:609 내지 1215
632	393	CGCCUUUUGAGACCCUGCAtt	1000	UGCAGGGUCUCAAAGGCGtc
632	394	AGCCUUUUGAGACCCUGCAtt	1001	UGCAGGGUCUCAAAGGCUtc
633	395	GCCUUUUGAGACCCUGCUGtt	1002	CAGCAGGGUCUCAAAGGCtt
634	396	CCUUUUGAGACCCUGCUGUtt	1003	ACAGCAGGGUCUCAAAGGct
634	397	CCUUUUGAGACCCUGCUGAtt	1004	UCAGCAGGGUCUCAAAGGct
635	398	CUUUUUGAGACCCUGCUGUctt	1005	GACAGCAGGGUCUCAAAGgc
635	399	CUUUUUGAGACCCUGCUGUAtt	1006	UACAGCAGGGUCUCAAAGgc
636	400	UUUUGAGACCCUGCUGUCCtt	1007	GGACAGCAGGGUCUCAAAGg
637	401	UUUGAGACCCUGCUGUCCctt	1008	GGGACAGCAGGGUCUCAAag
638	402	UUGAGACCCUGCUGUCCCAtt	1009	UGGGACAGCAGGGUCUCAAaa
639	403	UGAGACCCUGCUGUCCCAgtt	1010	CUGGGACAGCAGGGUCUCAA
640	404	GAGACCCUGCUGUCCCAgtt	1011	UCUGGGACAGCAGGGUCUCaa
641	405	AGACCCUGCUGUCCCAgAtt	1012	UUCUGGGACAGCAGGGUCUca
642	406	GACCCUGCUGUCCCAgAActt	1013	GUUCUGGGACAGCAGGGUctc
643	407	ACCCUGCUGUCCCAgAACttt	1014	GGUUCUGGGACAGCAGGGUct
643	408	ACCCUGCUGUCCCAgAACAtt	1015	UGUUCUGGGACAGCAGGGUct
644	409	CCCUGCUGUCCCAgAACAtt	1016	UGGUUCUGGGACAGCAGGGtc
645	410	CCUGCUGUCCCAgAACAGtt	1017	CUGGUUCUGGGACAGCAGGgt
646	411	CUGCUGUCCCAgAACAGGtt	1018	CCUGGUUCUGGGACAGCAGgg
647	412	UGCUGUCCCAgAACAGGGtt	1019	CCCUGGUUCUGGGACAGCAgg
648	413	UGCUGUCCCAgAACAGGAtt	1020	UCCUGGUUCUGGGACAGCAgg
648	414	GCUGUCCCAgAACAGGGAAtt	1021	UCCUGGUUCUGGGACAGCAg
649	415	CUGUCCCAgAACAGGGAGtt	1022	CUCCUGGUUCUGGGACAGca
650	416	UGUCCCAgAACAGGGAGGtt	1023	CCUCCUGGUUCUGGGACAgc
651	417	GUCCCAgAACAGGGAGGctt	1024	GCCUCCUGGUUCUGGGACag
652	418	UCCCAgAACAGGGAGGCAtt	1025	UGCCUCCUGGUUCUGGGAca
653	419	CCCAGAACAGGGAGGCAAtt	1026	UUGCCUCCUGGUUCUGGGac
654	420	CCAGAACAGGGAGGCAAGtt	1027	CUUGCCUCCUGGUUCUGGga

[0076]

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655	421	CAGAACCAGGGAGGCAAGAtt	1028	UCUUGCCUCCCUGGUUCUg
656	422	AGAACCAGGGAGGCAAGAct	1029	GUCUUGCCUCCCUGGUUCUg
657	423	GAACCAGGGAGGCAAGACtt	1030	GGUCUUGCCUCCCUGGUUct
658	424	AACCAGGGAGGCAAGACUtt	1031	AGGUCUUGCCUCCCUGGUUct
659	425	ACCAGGGAGGCAAGACCUUtt	1032	AAGGUCUUGCCUCCCUGGUtc
660	426	CCAGGGAGGCAAGACCUUctt	1033	GAAGGUCUUGCCUCCCUGGtt
661	427	CAGGGAGGCAAGACCUUCAtt	1034	UGAAGGUCUUGCCUCCCUGgt
662	428	AGGGAGGCAAGACCUUCAUtt	1035	AUGAAGGUCUUGCCUCCCUGg
663	429	GGGAGGCAAGACCUUCAUUtt	1036	AAUGAAGGUCUUGCCUCCctg
664	430	GGAGGCAAGACCUUCAUUGtt	1037	CAAUGAAGGUCUUGCCUCCct
665	431	GAGGCAAGACCUUCAUUGUtt	1038	ACAAUGAAGGUCUUGCCUCcc
666	432	AGGCAAGACCUUCAUUGUGtt	1039	CACAAUGAAGGUCUUGCCUcc
667	433	GGCAAGACCUUCAUUGUGGtt	1040	CCACAAUGAAGGUCUUGCCtc
668	434	GCAAGACCUUCAUUGUGGGtt	1041	CCCACAAUGAAGGUCUUGCct
669	435	CAAGACCUUCAUUGUGGGAtt	1042	UCCACAAUGAAGGUCUUGcc
670	436	AAGACCUUCAUUGUGGGAGtt	1043	CUCCACAAUGAAGGUCUUGc
671	437	AGACCUUCAUUGUGGGAGAtt	1044	UCUCCACAAUGAAGGUCUtg
672	438	GACCUUCAUUGUGGGAGActt	1045	GUCUCCACAAUGAAGGUctt
673	439	ACCUUCAUUGUGGGAGACtt	1046	GGUCUCCACAAUGAAGGUct
674	440	CCUUCAUUGUGGGAGACAtt	1047	UGGUCUCCACAAUGAAGGtc
675	441	CUUCAUUGUGGGAGACCAGtt	1048	CUGGUCUCCACAAUGAAGgt
676	442	UUCAUUGUGGGAGACCAGAtt	1049	UCUGGUCUCCACAAUGAAgg
677	443	UCAUUGUGGGAGACCAGAUtt	1050	AUCUGGUCUCCACAAUGAag
678	444	CAUUGUGGGAGACCAGAUctt	1051	GAUCUGGUCUCCACAAUGaa
679	445	AUUGUGGGAGACCAGAUcUtt	1052	AGAUCUGGUCUCCACAAUga
680	446	UUGUGGGAGACCAGAUcUctt	1053	GAGAUcUGGUCUCCACAAtg
681	447	UGUGGGAGACCAGAUcUctt	1054	GGAGAUcUGGUCUCCACAat
682	448	GUGGGAGACCAGAUcUcUtt	1055	AGGAGAUcUGGUCUCCACaa

[0077]

Ref Pos	SEQ ID NO	센스 가닥 (5'-->3') SEQ ID NOS:2 내지 608	SEQ ID NO	안티센스 가닥 (5'-->3') SEQ ID NOS:609 내지 1215
683	449	UGGGAGACCAGAUCCUUt	1056	AAGGAGAUUGGUCUCCAc
684	450	GGGAGACCAGAUCCUUCt	1057	GAAGGAGAUUGGUCUCCac
685	451	GGAGACCAGAUCCUUCGt	1058	CGAAGGAGAUUGGUCUCCa
686	452	GAGACCAGAUCCUUCGct	1059	GCGAAGGAGAUUGGUCUcc
687	453	AGACCAGAUCCUUCGCUt	1060	AGCGAAGGAGAUUGGUCUcc
688	454	GACCAGAUCCUUCGCGUt	1061	CAGCGAAGGAGAUUGGUct
689	455	ACCAGAUCCUUCGCGUAt	1062	UCAGCGAAGGAGAUUGGUct
690	456	CCAGAUCCUUCGCGUACt	1063	GUCAGCGAAGGAGAUUGGtc
691	457	CAGAUCCUUCGCGUGACU	1064	AGUCAGCGAAGGAGAUUGgt
692	458	AGAUCCUUCGCGUGACUA	1065	UAGUCAGCGAAGGAGAUUg
693	459	GAUCCUUCGCGUGACUAC	1066	GUAGUCAGCGAAGGAGAUtg
694	460	AUCCUUCGCGUGACUACA	1067	UGUAGUCAGCGAAGGAGAU
695	461	UCUCCUUCGCGUGACUACA	1068	UUGUAGUCAGCGAAGGAGAt
696	462	CUCCUUCGCGUGACUACA	1069	GUUGUAGUCAGCGAAGGAGat
697	463	UCCUUCGCGUGACUACA	1070	GGUUGUAGUCAGCGAAGGAga
698	464	CCUUCGCGUGACUACA	1071	AGGUUGUAGUCAGCGAAGGag
699	465	CUUCGCGUGACUACA	1072	CAGGUUGUAGUCAGCGAAGga
700	466	UUCGCGUGACUACA	1073	GCAGGUUGUAGUCAGCGAagg
701	467	UCGCGUGACUACA	1074	AGCAGGUUGUAGUCAGCGAag
702	468	CGCUGACUACA	1075	CAGCAGGUUGUAGUCAGCGaa
703	469	GCUGACUACA	1076	CCAGCAGGUUGUAGUCAGCga
704	470	CUGACUACA	1077	UCCAGCAGGUUGUAGUCAGcg
705	471	UGACUACA	1078	GUCCAGCAGGUUGUAGUCagc
706	472	GACUACA	1079	AGUCCAGCAGGUUGUAGUCag
707	473	ACUACA	1080	AAGUCCAGCAGGUUGUAGUca
708	474	CUACA	1081	CAAGUCCAGCAGGUUGUAGtc
709	475	UACA	1082	GCAAGUCCAGCAGGUUGUAg
710	476	ACA	1083	AGCAAGUCCAGCAGGUUGUag

[0078]

Ref Pos	SEQ ID NO	센스 가닥 (5'-->3') SEQ ID NOS:2 내지 608	SEQ ID NO	안티센스 가닥 (5'-->3') SEQ ID NOS:609 내지 1215
711	477	CAACCUGCUGGACUUGCUGt	1084	CAGCAAGUCCAGCAGGUUGta
712	478	AACCUGCUGGACUUGCUGCtt	1085	GCAGCAAGUCCAGCAGGUUgt
713	479	ACCUGCUGGACUUGCUGCUtt	1086	AGCAGCAAGUCCAGCAGGUtg
714	480	CCUGCUGGACUUGCUGCUGtt	1087	CAGCAGCAAGUCCAGCAGGtt
715	481	CUGCUGGACUUGCUGCUGAtt	1088	UCAGCAGCAAGUCCAGCAGgt
716	482	UGCUGGACUUGCUGCUGAUtt	1089	AUCAGCAGCAAGUCCAGCagg
717	483	GCUGGACUUGCUGCUGAUCCtt	1090	GAUCAGCAGCAAGUCCAGCag
718	484	CUGGACUUGCUGCUGAUCCtt	1091	GGAUCAGCAGCAAGUCCAGca
719	485	UGGACUUGCUGCUGAUCCAtt	1092	UGGAUCAGCAGCAAGUCCAgc
720	486	GGACUUGCUGCUGAUCCAUtt	1093	AUGGAUCAGCAGCAAGUCCag
721	487	GACUUGCUGCUGAUCCAUGtt	1094	CAUGGAUCAGCAGCAAGUCca
722	488	ACUUGCUGCUGAUCCAUGAtt	1095	UCAUGGAUCAGCAGCAAGUcc
723	489	CUUGCUGCUGAUCCAUGAGtt	1096	CUCAUGGAUCAGCAGCAAGtc
724	490	UUGCUGCUGAUCCAUGAGGtt	1097	CCUCAUGGAUCAGCAGCAagt
725	491	UGCUGCUGAUCCAUGAGGUtt	1098	ACCUCAUGGAUCAGCAGCAag
726	492	GCUGCUGAUCCAUGAGGUCCtt	1099	GACCUCAUGGAUCAGCAGCaa
727	493	CUGCUGAUCCAUGAGGUCCtt	1100	GGACCUCAUGGAUCAGCAGca
728	494	UGCUGAUCCAUGAGGUCCUtt	1101	AGGACCUCAUGGAUCAGCAgc
729	495	GCUGAUCCAUGAGGUCCUAtt	1102	UAGGACCUCAUGGAUCAGCag
730	496	CUGAUCCAUGAGGUCCUAGtt	1103	CUAGGACCUCAUGGAUCAGca
731	497	UGAUCCAUGAGGUCCUAGCtt	1104	GCUAGGACCUCAUGGAUCAgc
732	498	GAUCCAUGAGGUCCUAGCCtt	1105	GGCUAGGACCUCAUGGAUCag
733	499	AUCCAUGAGGUCCUAGCCCtt	1106	GGGCUAGGACCUCAUGGAUca
750	500	CCCUGGCUGCCUGGAUGCGtt	1107	CGCAUCCAGGCAGCCAGGGgc
751	501	CCUGGCUGCCUGGAUGCGUtt	1108	ACGCAUCCAGGCAGCCAGgg
752	502	CUGGCUGCCUGGAUGCGUUtt	1109	AACGCAUCCAGGCAGCCAGgg
753	503	UGGCUGCCUGGAUGCGUUCtt	1110	GAACGCAUCCAGGCAGCCAgg
754	504	GGCUGCCUGGAUGCGUUCctt	1111	GGAACGCAUCCAGGCAGCCag

[0079]

Ref Pos	SEQ ID NO	센스 가닥 (5'-->3') SEQ ID NOS:2 내지 608	SEQ ID NO	안티센스 가닥 (5'-->3') SEQ ID NOS:609 내지 1215
755	505	GCUGCCUGGAUGCGUCCctt	1112	GGGAACGCAUCCAGGCAGCca
773	506	CCCUGCUCUCAGCAUAUGUtt	1113	ACAUAUGCUGAGAGCAGGg
774	507	CCUGCUCUCAGCAUAUGUGtt	1114	CACAUAUGCUGAGAGCAGGg
775	508	CUGCUCUCAGCAUAUGUGGtt	1115	CCACAUAUGCUGAGAGCAGg
776	509	UGCUCUCAGCAUAUGUGGtt	1116	CCCACAUAUGCUGAGAGCAg
793	510	GGGCGCCUCAGUGCCCGGctt	1117	GCCGGGCACUGAGGCGCCca
794	511	GGCGCCUCAGUGCCCGGctt	1118	GGCCGGGCACUGAGGCGCCc
795	512	GCGCCUCAGUGCCCGGctt	1119	GGGCGGGGCACUGAGGCGcc
796	513	CGCCUCAGUGCCCGGCCAtt	1120	UGGGCGGGGCACUGAGGCGcc
797	514	GCCUCAGUGCCCGGCCAAtt	1121	UUGGGCGGGGCACUGAGGcg
798	515	CCUCAGUGCCCGGCCAAGtt	1122	CUUGGGCGGGGCACUGAGGcg
799	516	CUCAGUGCCCGGCCAAGctt	1123	GCUUGGGCGGGGCACUGAGgc
800	517	UCAGUGCCCGGCCAAGCUtt	1124	AGCUUGGGCGGGGCACUAgg
801	518	CAGUGCCCGGCCAAGCUCtt	1125	GAGCUUGGGCGGGGCACUgag
802	519	AGUGCCCGGCCAAGCUCAtt	1126	UGAGCUUGGGCGGGGCACUga
803	520	GUGCCCGGCCAAGCUCAAtt	1127	UUGAGCUUGGGCGGGGCActg
804	521	UGCCCGGCCAAGCUCAAGtt	1128	CUUGAGCUUGGGCGGGGAct
805	522	GCCCGGCCAAGCUCAAGGtt	1129	CCUUGAGCUUGGGCGGGGac
806	523	CCCGGCCAAGCUCAAGGctt	1130	GCCUUGAGCUUGGGCGGGca
807	524	CCGGCCCAAGCUCAAGGctt	1131	GGCCUUGAGCUUGGGCGGgc
808	525	CGGCCCAAGCUCAAGGCCUtt	1132	AGGCCUUGAGCUUGGGCGgg
809	526	GGCCCAAGCUCAAGGCCUtt	1133	AAGGCCUUGAGCUUGGGCGg
810	527	GCCCAAGCUCAAGGCCUctt	1134	GAAGGCCUUGAGCUUGGGCcg
811	528	CCCAAGCUCAAGGCCUCCtt	1135	GGAAGGCCUUGAGCUUGGGcc
812	529	CCAAGCUCAAGGCCUCCUtt	1136	AGGAAGGCCUUGAGCUUGGgc
813	530	CAAGCUCAAGGCCUCCUGtt	1137	CAGGAAGGCCUUGAGCUUGg
814	531	AAGCUCAAGGCCUCCUGGtt	1138	CCAGGAAGGCCUUGAGCUUg
815	532	AGCUCAAGGCCUCCUGGctt	1139	GCCAGGAAGGCCUUGAGCUtg

[0080]

Ref Pos	SEQ ID NO	센스 가닥 (5'-->3') SEQ ID NOS:2 내지 608	SEQ ID NO	안티센스 가닥 (5'-->3') SEQ ID NOS:609 내지 1215
816	533	GCUCAAGGCCUCCUGGCCttt	1140	GGCCAGGAAGGCCUUGAGCttt
817	534	CUCAAGGCCUCCUGGCCUttt	1141	AGGCCAGGAAGGCCUUGAGctt
818	535	UCAAGGCCUCCUGGCCUctt	1142	GAGGCCAGGAAGGCCUUGAgc
819	536	CAAGGCCUCCUGGCCUCCttt	1143	GGAGGCCAGGAAGGCCUUGAgg
820	537	AAGGCCUCCUGGCCUCCctt	1144	GGGAGGCCAGGAAGGCCUUGa
837	538	CCCUGAGUACGUGAACCUctt	1145	GAGGUUCACGUACUCAGGGga
838	539	CCUGAGUACGUGAACCUCCttt	1146	GGAGGUUCACGUACUCAGGgg
839	540	CUGAGUACGUGAACCUCCctt	1147	GGGAGGUUCACGUACUCAGgg
856	541	CCCAUCAUUGGCAACGGGAAtt	1148	UCCCGUUGCCAUUGAUGGGga
857	542	CCAUCAUUGGCAACGGGAAtt	1149	UUCCCGUUGCCAUUGAUGGgg
858	543	CAUCAUUGGCAACGGGAAAtt	1150	UUUCCCGUUGCCAUUGAUGgg
859	544	AUCAUUGGCAACGGGAAACttt	1151	GUUUCCCGUUGCCAUUGAUgg
860	545	UCAUUGGCAACGGGAAACAtt	1152	UGUUCCCGUUGCCAUUGAtg
861	546	CAAUGGCAACGGGAAACAGttt	1153	CUGUUCCCGUUGCCAUUGat
862	547	AAUGGCAACGGGAAACAGUttt	1154	ACUGUUCCCGUUGCCAUUGa
863	548	AUGGCAACGGGAAACAGUGttt	1155	CACUGUUCCCGUUGCCAUt
864	549	UGGCAACGGGAAACAGUGAtt	1156	UCACUGUUCCCGUUGCCAAtt
865	550	GGCAACGGGAAACAGUGAGttt	1157	CUCACUGUUCCCGUUGCCat
866	551	GCAACGGGAAACAGUGAGGttt	1158	CCUCACUGUUCCCGUUGCca
867	552	CAACGGGAAACAGUGAGGGttt	1159	CCCUCACUGUUCCCGUUGcc
868	553	AACGGGAAACAGUGAGGGUttt	1160	ACCCUCACUGUUCCCGUUGc
869	554	ACGGGAAACAGUGAGGGUUttt	1161	AACCCUCACUGUUCCCGUt
870	555	CGGGAAACAGUGAGGGUUGttt	1162	CAACCCUCACUGUUCCCGtt
871	556	GGGAAACAGUGAGGGUUGGttt	1163	CCAACCCUCACUGUUCCCGt
872	557	GGAAACAGUGAGGGUUGGGttt	1164	CCCAACCCUCACUGUUCCcg
891	558	GGGACUCUGAGCGGGAGGCttt	1165	GCCUCCCGCUCAGAGUCCcc
892	559	GGACUCUGAGCGGGAGGCAttt	1166	UGCCUCCCGCUCAGAGUCCc
894	560	ACUCUGAGCGGGAGGCAGAtt	1167	UCUGCCUCCCGCUCAGAGUcc

[0081]

Ref Pos	SEQ ID NO	센스 가닥 (5'-->3') SEQ ID NOS:2 내지 608	SEQ ID NO	안티센스 가닥 (5'-->3') SEQ ID NOS:609 내지 1215
896	561	UCUGAGCGGGAGGCAGAGUtt	1168	ACUCUGCCUCCCGCUCAGAg
897	562	CUGAGCGGGAGGCAGAGUUtt	1169	AACUCUGCCUCCCGCUCAGag
898	563	UGAGCGGGAGGCAGAGUUUtt	1170	AAACUCUGCCUCCCGCUCAGa
899	564	GAGCGGGAGGCAGAGUUUGtt	1171	CAAACUCUGCCUCCCGCUCag
900	565	AGCGGGAGGCAGAGUUUGCtt	1172	GCAAACUCUGCCUCCCGCUca
901	566	GCGGGAGGCAGAGUUUGCCtt	1173	GGCAAACUCUGCCUCCCGCtc
902	567	CGGGAGGCAGAGUUUGCCUtt	1174	AGGCAAACUCUGCCUCCCGct
903	568	GGGAGGCAGAGUUUGCCUUtt	1175	AAGGCAAACUCUGCCUCCGc
904	569	GGAGGCAGAGUUUGCCUUCtt	1176	GAAGGCAAACUCUGCCUCCg
905	570	GAGGCAGAGUUUGCCUUCct	1177	GGAAGGCAAACUCUGCCUCc
906	571	AGGCAGAGUUUGCCUUCUtt	1178	AGGAAGGCAAACUCUGCCUcc
907	572	GGCAGAGUUUGCCUUCUUtt	1179	AAGGAAGGCAAACUCUGCct
908	573	GCAGAGUUUGCCUUCUUUtt	1180	AAAGGAAGGCAAACUCUGCct
909	574	CAGAGUUUGCCUUCUUUCtt	1181	GAAAGGAAGGCAAACUCUGcc
910	575	AGAGUUUGCCUUCUUUCUtt	1182	AGAAAGGAAGGCAAACUCUgc
911	576	GAGUUUGCCUUCUUUCUCtt	1183	GAGAAAGGAAGGCAAACUCtg
912	577	AGUUUGCCUUCUUUCUCct	1184	GGAGAAAGGAAGGCAAACUct
913	578	GUUUGCCUUCUUUCUCCAtt	1185	UGGAGAAAGGAAGGCAAACtc
914	579	UUUGCCUUCUUUCUCCAGtt	1186	CUGGAGAAAGGAAGGCAAAct
915	580	UUGCCUUCUUUCUCCAGGtt	1187	CCUGGAGAAAGGAAGGCAAac
916	581	UGCCUUCUUUCUCCAGGAtt	1188	UCCUGGAGAAAGGAAGGCAaa
917	582	GCCUUCUUUCUCCAGGACtt	1189	GUCCUGGAGAAAGGAAGGCaa
918	583	CCUUCUUUCUCCAGGACct	1190	GGUCCUGGAGAAAGGAAGGca
919	584	CUUCCUUUCUCCAGGACAtt	1191	UGGUCCUGGAGAAAGGAAGgc
920	585	UUCUUUCUCCAGGACCAAtt	1192	UUGGUCCUGGAGAAAGGAagg
921	586	UCCUUUCUCCAGGACCAUtt	1193	AUUGGUCCUGGAGAAAGGAag
922	587	CCUUUCUCCAGGACCAUAAtt	1194	UAUUGGUCCUGGAGAAAGGaa
923	588	CUUUCUCCAGGACCAUAAAtt	1195	UUAUUGGUCCUGGAGAAAGga

[0082]

Ref Pos	SEQ ID NO	센스 가닥 (5'-->3')	SEQ ID NO	안티센스 가닥 (5'-->3')
		SEQ ID NOS:2 내지 608		SEQ ID NOS:609 내지 1215
924	589	UUUCUCCAGGACCAUAAAAtt	1196	UUUAUUGGUCCUGGAGAAAgg
925	590	UUCUCCAGGACCAUAAAAAtt	1197	UUUUUUGGUCCUGGAGAAag
926	591	UCUCCAGGACCAUAAAAUtt	1198	AUUUUUUGGUCCUGGAGAAa
927	592	CUCCAGGACCAUAAAAUUtt	1199	AAUUUUUUGGUCCUGGAGaa
928	593	UCCAGGACCAUAAAAUUUtt	1200	AAAUUUUUGGUCCUGGAGa
929	594	CCAGGACCAUAAAAUUUCtt	1201	GAAAUUUUUGGUCCUGGag
930	595	CAGGACCAUAAAAUUUCUtt	1202	AGAAAUUUUUGGUCCUGga
931	596	AGGACCAUAAAAUUUCUAtt	1203	UAGAAAUUUUUGGUCCUgg
932	597	GGACCAUAAAAUUUCUAAtt	1204	UUAGAAAUUUUUGGUCCtg
933	598	GACCAUAAAAUUUCUAAGtt	1205	CUUAGAAAUUUUUGGUCCt
934	599	ACCAUAAAAUUUCUAAGAAtt	1206	UCUUAGAAAUUUUUGGUcc
935	600	CCAUAAAAUUUCUAAGAGtt	1207	CUCUUAGAAAUUUUUGGtc
936	601	CAUAAAAUUUCUAAGAGAtt	1208	UCUCUUAGAAAUUUUUGgt
937	602	AAUAAAAUUUCUAAGAGAGtt	1209	CUCUCUUAGAAAUUUUUGg
938	603	AUAAAAUUUCUAAGAGAGCtt	1210	GCUCUCUUAGAAAUUUUAUtg
939	604	UAAAAUUUCUAAGAGAGCUtt	1211	AGCUCUCUUAGAAAUUUUAAtt
940	605	AAAAUUUCUAAGAGAGCUAAtt	1212	UAGCUCUCUUAGAAAUUUUat
941	606	AAAUUUCUAAGAGAGCUAAtt	1213	UUAGCUCUCUUAGAAAUUUta
942	607	AAUUUCUAAGAGAGCUAAAAtt	1214	UUUAGCUCUCUUAGAAAUUtt
943	608	AUUUCUAAGAGAGCUAAAAAtt	1215	UUUUAGCUCUCUUAGAAAUtt

[0083]

[0084]

표 1 에 관한 기호설명: 대문자 A, G, C 및 U 는 각각 리보-A, 리보-G, 리보-C 및 리보-U 를 지칭한다. 소문자 a, g, c, t 는 각각 2'-데옥시-A, 2'-데옥시-G, 2'-데옥시-C 및 티미딘을 지칭한다.

[0085]

표 2: GST- π 에 관한 RNAi 분자 서열

ID	Ref Pos	SEQ ID NO	센스 가닥 (5'-->3')	SEQ ID NO	안티센스 가닥 (5'-->3')
			SEQ ID NOS:1216 내지 1280		SEQ ID NOS:1281 내지 1345
A1	652	1216	UCCAGAACCAGGGAGGCAtt	1281	UGCCUCCUGGUUCUGGGAc
A10	635	1217	CUUUUGAGACCCUGCUGUCtt	1282	GACAGCAGGGUCUCAAAGgc
A11	649	1218	CUGUCCAGAACCAGGGAGtt	1283	CUCCUGGUUCUGGGACAGca

[0086]

ID	Ref Pos	SEQ ID NO	센스 가닥 (5'-->3') SEQ ID NOS:1216 내지 1280	SEQ ID NO	안티센스 가닥 (5'-->3') SEQ ID NOS:1281 내지 1345
A12	650	1219	UGUCCCAGAACCCAGGGAGGtt	1284	CCUCCCUGGUUCUGGGACAgc
A13	631	1220	AAGCCUUUUGAGACCCUGCtt	1285	GCAGGGUCUCAAAGGCUUca
A14	638	1221	UUGAGACCCUGCUGUCCCAtt	1286	UGGGACAGCAGGGUCUCAAaa
A15	636	1222	UUUUGAGACCCUGCUGUCctt	1287	GGACAGCAGGGUCUAAAAGg
A16	640	1223	GAGACCCUGCUGUCCAGAtt	1288	UCUGGGACAGCAGGGUCUCaa
A17	332	1224	GCUGGAAGGAGGAGGUGGtt	1289	ACCACCUCUCCUUCAGCtc
A18	333	1225	CUGGAAGGAGGAGGUGGtt	1290	CACCACCUCUCCUUCAGct
A19	321	1226	UCAGGGCCAGAGCUGGAAGtt	1291	CUUCCAGCUCUGGCCCUGAtc
A2	639	1227	UGAGACCCUGCUGUCCAGtt	1292	CUGGGACAGCAGGGUCUCAaa
A20	323	1228	AGGGCCAGAGCUGGAAGGAtt	1293	UCCUUCAGCUCUGGCCCUGa
A21	331	1229	AGCUGGAAGGAGGAGGUGGtt	1294	CCACCUCUCCUUCAGCUct
A22	641	1230	AGACCCUGCUGUCCAGAAtt	1295	UUCUGGGACAGCAGGGUCUca
A23	330	1231	GAGCUGGAAGGAGGAGGUGtt	1296	CACCUCUCCUUCAGCUCtg
A25	647	1232	UGCUGUCCAGAACCCAGGGtt	1297	CCCUGGUUCUGGGACAGCAgg
A26	653	1233	CCCAGAACCAGGGAGGCAAtt	1298	UUGCCUCCUGGUUCUGGGac
A3	654	1234	CCAGAACCAGGGAGGCAAGtt	1299	CUUGCCUCCUGGUUCUGGga
A4	637	1235	UUUGAGACCCUGCUGUCctt	1300	GGGACAGCAGGGUCUAAAag
A5	642	1236	GACCCUGCUGUCCAGAActt	1301	GUUCUGGGACAGCAGGGUctc
A6	319	1237	GAUCAGGGCCAGAGCUGGAtt	1302	UCCAGCUCUGGCCCUGAUctg
A7	632	1238	AGCCUUUUGAGACCCUGCUtt	1303	AGCAGGGUCUCAAAGGCUtc
A8	633	1239	GCCUUUUGAGACCCUGCUGtt	1304	CAGCAGGGUCUCAAAGGctt
A9	634	1240	CCUUUUGAGACCCUGCUGUtt	1305	ACAGCAGGGUCUCAAAGGct
AG7	632	1241	CGCCUUUUGAGACCCUGCAtt	1306	UGCAGGGUCUCAAAGGCGtc
AK1	257	1242	CCUACACCGUGGUCUAUUUtt	1307	AAAUAGACCACGGUGUAGGgc
AK10	681	1243	UGUGGGAGACCAGAUUCctt	1308	GGAGAUUGGUCUCCACAat
AK11	901	1244	GCGGGAGGCAGAGUUUGCctt	1309	GGCAAACUCUGCCUCCCGctc
AK12	922	1245	CCUUUCUCCAGGACCAUAAtt	1310	UAUUGGUCCUGGAGAAAGGaa
AK13 /A24	643	1246	ACCCUGCUGUCCAGAACctt	1311	GGUUCUGGGACAGCAGGGUct

[0087]

ID	Ref Pos	SEQ ID NO	센스 가닥 (5'-->3') SEQ ID NOS:1216 내지 1280	SEQ ID NO	안티센스 가닥 (5'-->3') SEQ ID NOS:1281 내지 1345
AK2	267	1247	GGUCUAAUUUCCCAGUUCGAtt	1312	UCGAACUGGGAAAAGACCAc
AK3	512	1248	CCCUGGUGGACAUGGUGAAAtt	1313	UUCACCAUGUCCACCAGGGct
AK4	560	1249	ACAUCUCCCUCAUCUACACtt	1314	GUGUAGAUGAGGGAGAUGUat
AK5	593	1250	GCAAGGAUGACUAUGUGAAAtt	1315	UUCACAUAGUCAUCCUUGCcc
AK6	698	1251	CCUUCGCGUACUACAACCUtt	1316	AGGUUGUAGUCAGCGAAGGag
AK7	313	1252	CUGGCAGAUACAGGGCCAGAtt	1317	UCUGGCCUGAUCUGCCAGca
AK8	421	1253	GACGGAGACCUCACCCUGUtt	1318	ACAGGGUGAGGUCUCCGUCct
AK9	590	1254	CGGGCAAGGAUGACUAUGUtt	1319	ACAUAGUCAUCCUUGCCCCGcc
AU10	635	1255	CUUUUGAGACCCUGCUGUAtt	1320	UACAGCAGGGUCUAAAAGGgc
AU23	330	1256	GAGCUGGAAGGAGGAGGUAtt	1321	UACCUCUCCUCCUCCAGCUCtg
AU24	643	1257	ACCCUGCUGUCCAGAACAtt	1322	UGUUCUGGGACAGCAGGGUct
AU25	648	1258	UGCUGUCCAGAACAGGAtt	1323	UCCUGGUUCUGGGACAGCAGg
AU7	632	1259	AGCCUUUUGAGACCCUGCAtt	1324	UGCAGGGUCUAAAAGGCUtc
AU9	634	1260	CCUUUUGAGACCCUGCUGAtt	1325	UCAGCAGGGUCUAAAAGGct
B1	629	1261	UGAAGCCUUUUGAGACCCUtt	1326	AGGGUCUAAAAGGCUUCAgt
B10	627	1262	ACUGAAGCCUUUUGAGACCTt	1327	GGUCUAAAAGGCUUCAGUtg
B11	596	1263	AGGAUGACUAUGUGAAGGCtt	1328	GCCUUCACAUAGUCAUCCUtg
B12	597	1264	GGAUGACUAUGUGAAGGCAtt	1329	UGCCUUCACAUAGUCAUCCTt
B13	598	1265	GAUGACUAUGUGAAGGCACtt	1330	GUGCCUUCACAUAGUCAUCct
B14	564	1266	CUCCUCAUCUACACCAACtt	1331	GUUGGUGUAGAUGAGGGAGat
B2	630	1267	GAAGCCUUUUGAGACCCUGtt	1332	CAGGGUCUAAAAGGCUUCag
B3	563	1268	UCUCCUCAUCUACACCAAtt	1333	UUGGUGUAGAUGAGGGAGatg
B4	567	1269	CCUCAUCUACACCAACUAUtt	1334	AUAGUUGGUGUAGAUGAGGga
B5	566	1270	CCUCAUCUACACCAACUAAtt	1335	UAGUUGGUGUAGAUGAGGGag
B6	625	1271	CAACUGAAGCCUUUUGAGAtt	1336	UCUAAAAGGCUUCAGUUGcc
B7	626	1272	AACUGAAGCCUUUUGAGACtt	1337	GUCUAAAAGGCUUCAGUUGc
B8	628	1273	CUGAAGCCUUUUGAGACCTt	1338	GGGUCUAAAAGGCUUCAGtt
B9	565	1274	UCCUCAUCUACACCAACUtt	1339	AGUUGGUGUAGAUGAGGGAGa

[0088]

ID	Ref Pos	SEQ ID NO	센스 가닥 (5'-->3') SEQ ID NOS:1216 내지 1280	SEQ ID NO	안티센스 가닥 (5'-->3') SEQ ID NOS:1281 내지 1345
BG3	563	1275	GCUCCUCAUCUACACCAAtt	1340	UUGGUGUAGAUGAGGGAGCtg
BU02	631	1276	GAAGCCUUUUGAGACCCUAAtt	1341	UAGGGUCUAAAAGGCUUCag
BU10	627	1277	ACUGAAGCCUUUUGAGACAAtt	1342	UGUCUAAAAGGCUUCAGUtg
BU14	565	1278	CUCCUCAUCUACACCAAAAtt	1343	UUUGGUGUAGAUGAGGGAGat
BU4	567	1279	CCUCAUCUACACCAACUAAtt	1344	UUAGUUGGUGUAGAUGAGGga
C1-934	934	1280	ACCAAUAAAUUUUAAGAtt	1345	UCUUAGAAAUUUUAUUGGUcc

[0089]

[0090] 표 2 에 관한 기호설명: 대문자 A, G, C 및 U 는 각각 리보-A, 리보-G, 리보-C 및 리보-U 를 지칭한다. 소문자 a, g, c, t 는 각각 2'-데옥시-A, 2'-데옥시-G, 2'-데옥시-C 및 티미딘을 지칭한다.

[0091] 예를 들어, 본 발명의 siRNA 는 SEQ ID NO:1341 인 안티센스 가닥, 및 SEQ ID NO:1276 인 센스 가닥, 또는 이의 화학적으로 개질된 가닥을 가질 수 있다.

[0092] 예를 들어, 본 발명의 siRNA 는 SEQ ID NO:1305 인 안티센스 가닥, 및 SEQ ID NO:1240 인 센스 가닥, 또는 이

의 화학적으로 개질된 가닥을 가질 수 있다.

- [0093] 화학적 개질은 가닥 내의 임의의 위치 중의 임의의 뉴클레오타이드 상에 2'-OMe 치환기, 뿐 아니라 당연계에 공지된 다른 개질을 포함할 수 있다.
- [0094] GST- π 를 조정하고 악성 종양을 치료하기 위한 방법
- [0095] 본 발명의 구현예는 GST- π 및/또는 GST- π 단백질의 발현을 하향 조절 또는 억제하는데 사용될 수 있는 RNAi 분자를 제공할 수 있다.
- [0096] 일부 구현예에서, 본 발명의 RNAi 분자는 악성 종양과 같은 질환 또는 병태와 관련될 수 있는 GST- π 일배체형 다형성으로부터 비롯되는 GST- π 및/또는 GST- π 단백질의 발현을 하향 조절 또는 억제하는데 사용될 수 있다.
- [0097] GST- π 단백질 또는 mRNA 수준의 모니터링을 사용하여 유전자 침묵화를 특성규명하고, 본 발명의 화합물 및 조성물의 효능을 확인할 수 있다.
- [0098] 본 공개의 RNAi 분자는 개별적으로, 또는 다른 siRNA 와의 조합으로 하나 이상의 유전자의 발현을 조정하기 위해 사용될 수 있다.
- [0099] 본 공개의 RNAi 분자는 개별적으로, 또는 조합으로, 또는 다른 알려진 약물과 함께 악성 종양을 포함하는 GST- π 와 관련되는 질환의 예방 또는 치료 또는 병태 또는 장애의 증상의 완화를 위해 사용될 수 있다.
- [0100] 본 발명의 RNAi 분자는 GST- π 의 발현을 서열-특이적 방식으로 조정 또는 억제하는데 사용될 수 있다.
- [0101] 본 공개의 RNAi 분자는 가이드 가닥 (guide strand) 을 포함할 수 있으며, 가이드 가닥의 일련의 인접 뉴클레오타이드는 GST- π mRNA 에 적어도 부분적으로 상보적이다.
- [0102] 특정 양상에서, 악성 종양은 본 발명의 RNAi 분자를 사용하여 RNA 간섭에 의해 치료될 수 있다.
- [0103] 악성 종양의 치료는 적합한 세포 기반 모델, 뿐만 아니라 생체의 또는 생체내 동물 모델에서 특성규명될 수 있다.
- [0104] 악성 종양의 치료는 병든 조직의 세포에서의 GST- π mRNA 의 수준 또는 GST- π 단백질의 수준을 확인함으로써 특성규명될 수 있다.
- [0105] 악성 종양의 치료는 병든 장기 또는 조직의 비-침습적 의료 스캐닝에 의해 특성규명될 수 있다.
- [0106] 본 발명의 구현예는 그것을 필요로 하는 대상체에서 GST- π 관련되는 질환 또는 병태의 증상을 예방, 치료, 또는 완화하는 방법을 포함할 수 있다.
- [0107] 일부 구현예에서, 대상체에서 악성 종양의 증상을 예방, 치료, 또는 완화하는 방법은 대상체에게 본 발명의 RNAi 분자를 투여하여 대상체 또는 유기체에서 GST- π 유전자의 발현을 조정하는 것을 포함할 수 있다.
- [0108] 일부 구현예에서, 본 발명은 세포 또는 유기체를 본 발명의 RNAi 분자와 접촉시킴으로써 세포 또는 유기체에서 GST- π 유전자의 발현을 하향 조절하는 방법을 고려한다.
- [0109] RNA 간섭
- [0110] RNA 간섭 (RNA Interference) (RNAi) 은 짧은 간섭하는 RNA (siRNA) 에 의해 매개되는 동물에서의 서열-특정적 전사후 유전자 침묵화를 지칭한다. 예를 들어, Zamore et al., Cell, 2000, Vol. 101, pp. 25-33; Fire et al., Nature, 1998, Vol. 391, pp. 806811; Sharp, Genes & Development, 1999, Vol. 13, pp. 139-141 을 참고한다.
- [0111] 세포에서의 RNAi 반응은 이중가닥 RNA (dsRNA) 에 의해 유발될 수 있지만, 그 메커니즘은 아직 완전히 이해되지 않고 있다. 세포에서의 특정 dsRNA 는 다이스 (Dicer) 효소, 리보뉴클레아제 III 효소의 작용을 받을 수 있다. 예를 들어, Zamore et al., Cell, 2000, Vol. 101, pp. 25-33; Hammond et al., Nature, 2000, Vol. 404, pp. 293-296 을 참고한다. 다이스는 dsRNA 를 dsRNA 의 더 짧은 조각인 siRNA 로 가공할 수 있다.
- [0112] 일반적으로, siRNA 는 약 21 내지 약 23 개 뉴클레오타이드 길이일 수 있고, 약 19 개 뉴클레오타이드 길이의 염기쌍 듀플렉스 영역을 포함할 수 있다.
- [0113] RNAi 은 RNA 유도되는 침묵화 복합체 (RNA induced silencing complex) (RISC) 로서 알려진 엔도뉴클레아제 복

합체를 수반한다. siRNA 는 RISC 복합체에 진입하여 siRNA 듀플렉스의 안티센스 가닥에 상보적인 서열을 갖는 단일가닥 RNA 표적의 절단을 매개하는 안티센스 또는 가이드 가닥을 갖는다. siRNA 의 다른 가닥은 패신저 가닥 (passenger strand) 이다. 표적 RNA 의 절단은 siRNA 듀플렉스의 안티센스 가닥에 상보적인 영역의 중간에서 일어난다. 예를 들어, Elbashir et al., Genes & Development, 2001, Vol. 15, pp. 188-200 을 참고한다.

- [0114] 본원에서 사용되는 바와 같이, 용어 "센스 가닥" 은 siRNA 분자의 대응하는 안티센스 가닥의 적어도 일부분에 부분적으로 또는 전체적으로 상보적인 siRNA 분자의 뉴클레오티드 서열을 지칭한다. siRNA 분자의 센스 가닥은 표적 핵산 서열과 상동성을 갖는 핵산 서열을 포함할 수 있다.
- [0115] 본원에서 사용되는 바와 같이, 용어 "안티센스 가닥" 은 표적 핵산 서열의 적어도 일부분에 부분적으로 또는 전체적으로 상보적인 siRNA 분자의 뉴클레오티드 서열을 지칭한다. siRNA 분자의 안티센스 가닥은 siRNA 분자의 대응하는 센스 가닥의 적어도 일부분에 상보적인 핵산 서열을 포함할 수 있다.
- [0116] RNAi 분자는 RNA 간섭을 서열-특이적 방식으로 매개함으로써 유전자 발현을 하향 조절 또는 녹다운할 수 있다. 예를 들어, Zamore et al., Cell, 2000, Vol. 101, pp. 25-33; Elbashir et al., Nature, 2001, Vol. 411, pp. 494-498; Kreutzer et al., WO2000/044895; Zernicka-Goetz et al., WO2001/36646; Fire et al., WO1999/032619; Plaetinck et al., WO2000/01846; Mello et al., WO2001/029058 을 참고한다.
- [0117] 본원에서 사용되는 바와 같이, 유전자 발현에 관한 용어들 "억제," "하향-조절," 또는 "감소" 는 유전자의 발현, 또는 하나 이상의 단백질을 인코딩하는 mRNA 분자의 수준, 또는 인코딩된 단백질 중 하나 이상의 활성이 본 발명의 RNAi 분자 또는 siRNA 의 부재시에 관찰되는 것보다 아래로 감소되는 것을 의미한다. 예를 들어, 발현의 수준, mRNA 의 수준, 또는 인코딩된 단백질 활성의 수준은 본 발명의 RNAi 분자 또는 siRNA 의 부재시에 관찰되는 것보다 적어도 1%, 또는 적어도 10%, 또는 적어도 20%, 또는 적어도 50%, 또는 적어도 90%, 또는 그 이상 만큼 감소될 수 있다.
- [0118] RNAi 분자는 또한 바이러스 유전자 발현을 녹다운하고, 그에 따라 바이러스 복제에 영향을 미치는데 사용될 수 있다.
- [0119] RNAi 분자는 별개의 폴리뉴클레오티드 가닥: 센스 가닥 또는 패신저 가닥, 및 안티센스 가닥 또는 가이드 가닥 으로부터 만들어질 수 있다. 가이드 및 패신저 가닥은 적어도 부분적으로 상보적이다. 가이드 가닥 및 패신저 가닥은 약 15 내지 약 49 개의 염기쌍을 갖는 듀플렉스 영역을 형성할 수 있다.
- [0120] 일부 구현예에서, siRNA 의 듀플렉스 영역은 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 또는 49 개의 염기쌍을 가질 수 있다.
- [0121] 특정 구현예에서, RNAi 분자는 RISC 복합체에서 활성일 수 있으며, RISC 에 관해 활성인 듀플렉스 영역의 길이를 갖는다.
- [0122] 추가 구현예에서, RNAi 분자는 다이스 기질로서 활성이어서, RISC 복합체에서 활성일 수 있는 RNAi 분자로 전환될 수 있다.
- [0123] 일부 양상에서, RNAi 분자는 상보적 가이드 및 패신저 서열 부분을 긴 분자의 대향하는 말단들에 가질 수 있으며, 그에 따라 분자는 상보적 서열 부분들로 듀플렉스 영역을 형성할 수 있고, 가닥들은 듀플렉스 영역의 하나의 말단에 뉴클레오티드 또는 비-뉴클레오티드 링커에 의해 연결된다. 예를 들어, 헤어핀 배열, 또는 스템 및 루프 배열. 가닥들과의 링커 상호작용은 공유 결합 또는 비-공유 상호작용일 수 있다.
- [0124] 본 공개의 RNAi 분자는 핵산의 센스 영역을 핵산의 안티센스 영역에 연결시키는 뉴클레오티드, 비-뉴클레오티드, 또는 혼합된 뉴클레오티드/비-뉴클레오티드 링커를 포함할 수 있다. 뉴클레오티드 링커는 2 개 이상의 뉴클레오티드 길이, 예를 들어 약 3, 4, 5, 6, 7, 8, 9, 또는 10 개 뉴클레오티드 길이의 링커일 수 있다. 뉴클레오티드 링커는 핵산 애타머 (aptamer) 일 수 있다. 본원에서 사용되는 바와 같은 "애타머" 또는 "핵산 애타머" 는 표적 분자에 특이적으로 결합하는 핵산 분자를 지칭하며, 여기서 상기 핵산 분자는 그것의 자연적 환경에서 표적 분자에 의해 인지되는 서열을 포함하는 서열을 갖는다. 대안적으로, 애타머는 표적 분자에 결합하는 핵산 분자일 수 있으며, 여기에서 표적 분자는 핵산에 자연적으로 결합하지 않는다. 예를 들어, 애타머는 단백질의 리간드-결합 도메인에 결합하여, 이로써 천연 발생 리간드와 단백질의 상호작용을 방지하는데 사용될 수 있다. 예를 들어, Gold et al., Annu Rev Biochem, 1995, Vol. 64, pp. 763-797; Brody et al., J. Biotechnol., 2000, Vol. 74, pp. 5-13; Hermann et al., Science, 2000, Vol. 287, pp.

820-825 를 참고한다.

- [0125] 비-뉴클레오타이드 링커의 예는 무염기성 뉴클레오타이드, 폴리에테르, 폴리아민, 폴리아미드, 펩티드, 탄수화물, 지질, 폴리탄화수소, 또는 다른 폴리머 화합물, 예를 들어 폴리에틸렌 글리콜 에컨대 2 내지 100 개의 에틸렌 글리콜 단위체를 갖는 것들을 포함한다. 일부 예가 Seela et al., Nucleic Acids Research, 1987, Vol. 15, pp. 3113-3129; Cload et al., J. Am. Chem. Soc., 1991, Vol. 113, pp. 6324-6326; Jaeschke et al., Tetrahedron Lett., 1993, Vol. 34, pp. 301; Arnold et al., WO1989/002439; Usman et al., WO1995/006731; Dudycz et al., WO1995/011910, 및 Ferentz et al., J. Am. Chem. Soc., 1991, Vol. 113, pp. 4000-4002 에 기재되어 있다.
- [0126] RNAi 분자는 듀플렉스 영역으로부터의 오버행을 하나 이상 가질 수 있다. 오버행은 비-염기쌍, 단일 가닥 영역이며, 1 내지 8 개 뉴클레오타이드 길이, 또는 그 이상일 수 있다. 오버행은 3'-말단 오버행일 수 있으며, 여기서 가닥의 3'-말단은 1 내지 8 개 뉴클레오타이드의 단일 가닥 영역을 갖는다. 오버행은 5'-말단 오버행일 수 있으며, 여기서 가닥의 5'-말단은 1 내지 8 개 뉴클레오타이드의 단일 가닥 영역을 갖는다.
- [0127] RNAi 분자의 오버행은 동일한 길이를 가질 수 있거나, 또는 상이한 길이를 가질 수 있다.
- [0128] RNAi 분자는 하나 이상의 블런트 엔드를 가질 수 있으며, 여기에서 듀플렉스 영역은 오버행으로 끝나지 않고, 가닥들은 듀플렉스 영역의 말단까지 염기쌍을 이룬다.
- [0129] 본 공개의 RNAi 분자는 하나 이상의 블런트 엔드를 가질 수 있거나, 또는 하나 이상의 오버행을 가질 수 있거나, 또는 블런트 엔드와 오버행 말단의 조합을 가질 수 있다.
- [0130] RNAi 분자의 가닥의 5'-말단은 블런트 엔드에 있을 수 있거나, 또는 오버행에 있을 수 있다. RNAi 분자의 가닥의 3'-말단은 블런트 엔드에 있을 수 있거나, 또는 오버행에 있을 수 있다.
- [0131] RNAi 분자의 가닥의 5'-말단은 블런트 엔드에 있을 수 있으며, 한편 3'-말단은 오버행에 있다. RNAi 분자의 가닥의 3'-말단은 블런트 엔드에 있을 수 있으며, 한편 5'-말단은 오버행에 있다.
- [0132] 일부 구현예에서, RNAi 분자의 양쪽 말단은 블런트 엔드이다.
- [0133] 추가 구현예에서, RNAi 분자의 양쪽 말단은 오버행을 갖는다.
- [0134] 5'- 및 3'-말단의 오버행은 상이한 길이를 가질 수 있다.
- [0135] 특정 구현예에서, RNAi 분자는 블런트 엔드를 가질 수 있으며, 여기에서 안티센스 가닥의 5'-말단 및 센스 가닥의 3'-말단은 어떠한 오버행 뉴클레오타이드도 갖지 않는다.
- [0136] 추가 구현예에서, RNAi 분자는 블런트 엔드를 가질 수 있으며, 여기에서 안티센스 가닥의 3'-말단 및 센스 가닥의 5'-말단은 어떠한 오버행 뉴클레오타이드도 갖지 않는다.
- [0137] RNAi 분자는 듀플렉스 영역의 염기 쌍형성에서 미스매치를 가질 수 있다.
- [0138] RNAi 분자의 오버행에서의 임의의 뉴클레오타이드는 데옥시리보뉴클레오타이드, 또는 리보뉴클레오타이드일 수 있다.
- [0139] 하나 이상의 데옥시리보뉴클레오타이드는 5'-말단에 있을 수 있으며, 여기에서 RNAi 분자의 다른 가닥의 3'-말단은 오버행을 갖지 않을 수 있거나, 또는 데옥시리보뉴클레오타이드 오버행을 갖지 않을 수 있다.
- [0140] 하나 이상의 데옥시리보뉴클레오타이드는 3'-말단에 있을 수 있으며, 여기에서 RNAi 분자의 다른 가닥의 5'-말단은 오버행을 갖지 않을 수 있거나, 또는 데옥시리보뉴클레오타이드 오버행을 갖지 않을 수 있다.
- [0141] 일부 구현예에서, RNAi 분자의 오버행 뉴클레오타이드 중 하나 이상, 또는 전부는 2'-데옥시리보뉴클레오타이드일 수 있다.
- [0142] 다이어서 기질 RNAi 분자
- [0143] 일부 양상에서, RNAi 분자는 가공되어 RISC 활성 RNAi 분자를 초래할 수 있는, 다이어서 기질로서 적합한 길이를 가질 수 있다. 예를 들어, Rossi 등, US2005/0244858 을 참고한다.
- [0144] 다이어서 기질인 이중가닥 RNA (dsRNA) 은 다이어서에 의해 가공되어 활성 RNAi 분자를 생산하기에 충분한 길이를 가질 수 있고, 추가로 하기 특성 중 하나 이상을 포함할 수 있다: (i) 다이어서 기질 dsRNA 는 비대칭일 수 있으며, 예를 들어, 3' 오버행을 안티센스 가닥에 갖고, (ii) 다이어서 기질 dsRNA 는 활성 RNAi 분자로의 dsRNA 의

다이어서 결합 및 가공의 방향을 지시하는 개질된 3' 말단을 센스 가닥에 가질 수 있다.

- [0145] 특정 구현예에서, 다이어서 기질 dsRNA 에서 가장 긴 가닥은 24-30 개 뉴클레오타이드 길이일 수 있다.
- [0146] 다이어서 기질 dsRNA 는 대칭 또는 비대칭일 수 있다.
- [0147] 일부 구현예에서, 다이어서 기질 dsRNA 는 22-28 개 뉴클레오타이드의 센스 가닥 및 24-30 개 뉴클레오타이드의 안티센스 가닥을 가질 수 있다.
- [0148] 특정 구현예에서, 다이어서 기질 dsRNA 는 오버행을 안티센스 가닥의 3' 말단에 가질 수 있다.
- [0149] 추가 구현예에서, 다이어서 기질 dsRNA 는 센스 가닥 25 개 뉴클레오타이드 길이, 및 안티센스 가닥 27 개 뉴클레오타이드 길이와, 2 염기 3'-오버행을 가질 수 있다. 오버행은 1, 2 또는 3 개 뉴클레오타이드 길이일 수 있다. 센스 가닥은 또한 5' 인산염을 가질 수 있다.
- [0150] 비대칭 다이어서 기질 dsRNA 는 센스 가닥의 3'-말단에 리보뉴클레오타이드 중 2 개 대신에 데옥시리보뉴클레오타이드 2 개를 가질 수 있다.
- [0151] 다이어서 기질 dsRNA 의 센스 가닥은 약 22 내지 약 30, 또는 약 22 내지 약 28; 또는 약 24 내지 약 30; 또는 약 25 내지 약 30; 또는 약 26 내지 약 30; 또는 약 26 내지 29; 또는 약 27 내지 약 28 개 뉴클레오타이드 길이일 수 있다.
- [0152] 다이어서 기질 dsRNA 의 센스 가닥은 22, 23, 24, 25, 26, 27, 28, 29 또는 30 개 뉴클레오타이드 길이일 수 있다.
- [0153] 특정 구현예에서, 다이어서 기질 dsRNA 는 적어도 약 25 개 뉴클레오타이드 길이, 및 약 30 개 이하의 뉴클레오타이드 길이의 센스 및 안티센스 가닥을 가질 수 있다.
- [0154] 특정 구현예에서, 다이어서 기질 dsRNA 는 26 내지 29 개 뉴클레오타이드 길이의 센스 및 안티센스 가닥을 가질 수 있다.
- [0155] 특정 구현예에서, 다이어서 기질 dsRNA 는 27 개 뉴클레오타이드 길이의 센스 및 안티센스 가닥을 가질 수 있다.
- [0156] 다이어서 기질 dsRNA 의 센스 및 안티센스 가닥은 블런트 엔드인 경우와 같이 동일한 길이일 수 있거나, 또는 오버행을 갖는 경우와 같이 상이한 길이일 수 있거나, 또는 블런트 엔드 및 오버행을 가질 수 있다.
- [0157] 다이어서 기질 dsRNA 는 19, 20, 21, 22, 23, 24, 25, 26 또는 27 개 뉴클레오타이드 길이의 듀플렉스 영역을 가질 수 있다.
- [0158] 다이어서 기질 dsRNA 의 안티센스 가닥은 생물학적 조건 하에, 예컨대 진행 세포의 세포질 내에서, 센스 가닥의 서열의 적어도 일부분에 어닐링되는 임의의 서열을 가질 수 있다.
- [0159] 센스 및 안티센스 가닥을 갖는 다이어서 기질은 제 3 구조, 예컨대 링커 기 또는 링커 올리고뉴클레오타이드에 의해 연결될 수 있다. 링커는 dsRNA 의 2 개의 가닥을 연결시켜서, 예를 들어, 어닐링 후에 헤어핀이 형성된다.
- [0160] 다이어서 기질의 센스 및 안티센스 가닥은 일반적으로 상보적이지만, 염기 쌍형성에서 미스매치를 가질 수 있다.
- [0161] 일부 구현예에서, 다이어서 기질 dsRNA 는 비대칭이며, 센스 가닥은 22-28 개 뉴클레오타이드를 갖고 안티센스 가닥은 24-30 개 뉴클레오타이드를 가질 수 있다.
- [0162] 다이어서 기질 dsRNA 의 가닥 중 하나, 특히 안티센스 가닥의 영역은 적어도 19 개 뉴클레오타이드의 서열 길이를 가질 수 있으며, 여기서 이들 뉴클레오타이드는 안티센스 가닥의 3' 말단에 인접한 21-뉴클레오타이드 영역에 있고 표적 유전자로부터 생산된 RNA 의 뉴클레오타이드 서열에 충분히 상보적이다.
- [0163] 다이어서 기질 dsRNA 의 안티센스 가닥은 1 내지 9 개 리보뉴클레오타이드를 5'-말단에 가져서, 22-28 개 뉴클레오타이드의 길이를 초과할 수 있다. 안티센스 가닥이 21 개 뉴클레오타이드의 길이를 가질 때, 그 때 1-7 개 리보뉴클레오타이드, 또는 2-5 개 리보뉴클레오타이드, 또는 4 개 리보뉴클레오타이드가 3'-말단에 첨가될 수 있다. 첨가된 리보뉴클레오타이드는 임의의 서열을 가질 수 있다.
- [0164] 다이어서 기질 dsRNA 의 센스 가닥은 24-30 개 뉴클레오타이드를 가질 수 있다. 센스 가닥은 안티센스 가닥과 실질적으로 상보적이어서, 생물학적 조건 하에 안티센스 가닥에 어닐링될 수 있다.
- [0165] RNAi 분자의 사용 방법
- [0166] 본 발명의 핵산 분자 및 RNAi 분자는 분자의 직접 적용에 의해, 또는 담체 또는 희석제와 조합된 분자로, 세포

또는 조직에 전달될 수 있다.

[0167] 본 발명의 핵산 분자 및 RNAi 분자는 담체 또는 희석제, 또는 세포 내로의 진입을 보조하고, 촉진하거나 용이하게 하도록 작용하는 임의의 다른 전달 비히클, 예를 들어 바이러스 서열, 바이러스 물질, 또는 지질 또는 리포솜 제형과 분자의 직접 적용에 의해 세포, 조직, 기관 또는 대상체에 전달 또는 투여될 수 있다.

[0168] 본 발명의 핵산 분자 및 RNAi 분자는 양이온성 지질과 복합화되고, 리포솜 내에 패키징되고, 또는 다르게는 표적 세포 또는 조직에 전달될 수 있다. 핵산 또는 핵산 복합체는 생체외, 또는 생체내로 직접 전파 적용, 경피 적용 또는 주사를 통해 관련 조직에 국소 투여될 수 있다.

[0169] 전달 시스템은 예를 들어, 수성 및 비수성 겔, 크림, 에멀전, 마이크로에멀전, 리포솜, 연고, 수용액 및 비수용액, 로션, 에어로졸, 탄화수소 베이스 및 분말을 포함할 수 있으며, 가용화제 및 투과 증강제와 같은 부형제를 함유할 수 있다.

[0170] 본 개시물의 조성물 및 방법은, 핵산 분자의 발현을 허용하는 방식으로 본 발명의 하나 이상의 RNAi 분자를 인코딩하는 핵산 서열을 포함하는 발현 벡터를 포함할 수 있다.

[0171] 본 발명의 핵산 분자 및 RNAi 분자는 DNA 또는 RNA 벡터에 삽입된 전사 단위로부터 발현될 수 있다. 재조합 벡터는 DNA 플라스미드 또는 바이러스 벡터일 수 있다. 핵산 분자의 일시적 발현이 가능하도록 바이러스 벡터가 사용될 수 있다.

[0172] 예를 들어, 벡터는 듀플렉스의 RNAi 분자의 두 가닥 모두, 또는 자가 상보성이며 따라서 RNAi 분자를 형성하는 단일 핵산 분자를 인코딩하는 서열을 함유할 수 있다. 발현 벡터는 둘 이상의 핵산 분자를 인코딩하는 핵산 서열을 포함할 수 있다.

[0173] 핵산 분자는 진핵생물 프로모터로부터 세포 내에 발현될 수 있다. 당업자는 임의의 핵산이 적절한 DNA/RNA 벡터로부터 진핵생물 세포에서 발현될 수 있다는 것을 인지하고 있다.

[0174] 일부 양상에서, 발현 구축물에 의해 인코딩된 dsRNA 구축물의 전사를 위하여, 세포 내로 발현 구축물이 도입되도록 바이러스 구축물을 사용할 수 있다.

[0175] 지질 제형은 정맥내, 근육내, 또는 복강내 주사, 또는 경구 또는 흡입으로 또는 당업계에 공지되어 있는 다른 방법에 의해 동물에 투여될 수 있다.

[0176] 올리고뉴클레오타이드를 투여하기 위한 약학적으로 허용가능한 제형이 공지되어 있으며 사용될 수 있다.

[0177] 실시예

[0178] **실시예 1:** siRNA 녹다운 효력을 결정하기 위해 A549 세포주에서 시험관내 트랜스펙션을 수행했다. 표 3에 제시된 바와 같이, GST- π mRNA에 관한 투여량 의존적 녹다운을 siRNA와 함께 관찰했다.

[0179] 표 3: A549 세포주에서의 GST- π mRNA에 관한 투여량 의존적 녹다운

siRNA	IC50 (pM)
A9	27, 29
B2	121
B3	235
B4	229
B13	23, 34
BU02	21, 25, 34

[0180]

[0181] **실시예 2:** 시험관내 녹다운에 관한 프로토콜

[0182] 트랜스펙션 전 1 일에, 세포를 96-웰 플레이트에 10% FBS를 함유하는 100 μ l의 DMEM (HyClone Cat. # SH30243.01)을 함유하는 웰 마다 2×10^3 개의 세포를 플레이트팅하고, 공기 중에 5% CO₂의 가습된 분위기를 함유하는 37°C 인큐베이터에서 배양했다. 트랜스펙션 전에, 배지를 2% FBS를 함유하는 90 μ l의 Opti-MEM I 감소된 혈청 배지 (Life Technologies Cat. # 31985-070)로 교체했다. 그 후, 0.2 μ l의 리포펙타민

RNAiMax (Life Technologies Cat. # 13778-100) 를 5 분 동안 실온에서 $4.8 \mu\text{l}$ 의 Opti-MEM I 와 혼합했다. 그 후, $1 \mu\text{l}$ 의 siRNA 를 $4 \mu\text{l}$ 의 Opti-MEM I 와 혼합하고, LF2000 용액과 조합하고, 볼텍스하지 않으면서 부드럽게 혼합했다. 실온에서 5 분 동안 기다렸다. 혼합물을 추가의 10 분 동안 실온에서 인큐베이션하여 RNA-RNAiMax 복합체가 형성되게 했다. 또한, $10 \mu\text{l}$ 의 RNA-RNAiMax 복합체를 웰에 첨가하고, 플레이트를 손으로 부드럽게 진탕했다. 세포를 공기 중에 5% CO_2 의 가습된 분위기를 함유하는 37°C 인큐베이터에서 2 시간 동안 인큐베이션했다. 배지를 2% FBS 를 함유하는 신선한 Opti-MEM I 감소된 혈청 배지 (Life Technologies Cat. # 31985-070) 로 교체했다. 트랜스펙션 후 24 시간에, 세포를 빙랭 PBS 로 1 회 세정했다. 세포를 $50 \mu\text{l}$ 의 Cell-to-Ct 세포용해 버퍼 (Life Technologies Cat. # 4391851 C) 로 5-30 분 동안 실온에서 용해했다. $5 \mu\text{l}$ 의 정지액을 첨가하고, 그것을 2 분 동안 실온에서 인큐베이션했다. mRNA 수준을 RT-qPCR 에 의해 TAQMAN 을 이용하여 즉시 측정했다. 대안적으로는, 샘플을 -80°C 에서 냉동하고 나중에 분석할 수 있었다.

[0183] **실시예 3:** 도 2 는 GST- π siRNA 에 관한 생체 내 녹다운 효력을 보여준다. 도 2 에 제시된 바와 같이, GST- π mRNA 의 투여량 의존적 녹다운을 GST- π 를 표적으로 하는 BU02 siRNA 와 함께 생체 내에서 관찰했다.

[0184] **실시예 4:** 도 3 은 siRNA 를 표적으로 하는 GST- π 에 의한 세포 증식의 억제를 보여준다. 도 3 에 제시된 바와 같이, 증식의 투여량-의존적 억제를 GST- π 를 표적으로 하는 siRNA 와 함께 시험관 내에서 A549 세포주에서 관찰했다.

[0185] **실시예 5:** 도 4 는 GST- π siRNA (BU02) 에 관한 종양 억제 효과를 보여준다. 췌장암 이종이식 모델을 GST- π 를 표적으로 하는 0.75 mg/kg 의 siRNA 에서 비교적 낮은 투여량으로 이용했다. 제 28 일에 GST- π siRNA 는 유의미하고 예상외로 유리한 종양 억제 효능을 입증했다.

[0186] 본 실험에서, A549 및 PANC-1 세포주를 ATCC 로부터 입수했다. 세포 현탁액을 주사를 위해 얼음 해동된 BD 매트릭셀과 1:1 비로 잘 혼합했다. 각각의 마우스 (무흉선 누드 암컷 마우스, 6 내지 8 주, Charles River) 에, 25 G 바늘 및 주사기 (마우스 당 1 점종물) 를 사용하여 2×10^6 (A549) 또는 2.5×10^6 (PANC-1) 세포의 점종물 0.1 ml 으로 우측면에 피하 점종했다. 점종을 위해 마우스를 마취했다. 성립된 종양이 대략 $250 - 350 \text{ mm}^3$ (A549) 또는 $150 - 250 \text{ mm}^3$ (PANC-1) 에 도달한 날에, 동물을 꼬리 정맥을 통해 볼루스 주사에 적용했다. 동물을 과다투여된 CO_2 에 의해 희생시키고, 종양을 투약 후 상이한 시점에 해부했다. 종양을 먼저 습윤 칭량한 다음, GST- π 녹다운의 측정, siRNA 의 생물분포 (biodistribution), 및 바이오마커 분석을 위해 3 부분으로 분리했다. 샘플을 액체 질소에 스냅 동결하고, 생분석을 위해 처리할 준비가 될 때까지 -80°C 에서 저장했다.

[0187] **실시예 6: 동소이식 A549 폐암 마우스 모델.** 본 발명의 GST- π siRNA 는 생체내에서 동소이식 (orthotopic) 폐암 종양의 현저한 감소를 나타낼 수 있다. 이 실시예에서, GST- π siRNA 는 생체내에서 리포좀 제형으로 무흉선 누드 마우스의 동소이식 폐암 종양에 투여될 때 유전자 녹다운 효력을 제공했다.

[0188] 일반적으로, 동소이식 종양 모델은 약물 효능 및 효력에 관한 직접적인 임상 관련성, 뿐만 아니라 개선된 예측의 능력을 나타낼 수 있다. 동소이식 종양 모델에서, 종양 세포는 세포가 유래되는 장기와 동일한 종류의 장기 내로 직접적으로 이식된다.

[0189] 처리 그룹 및 비히클 컨트롤 그룹에 관해 부검시 측정된 최종 원발성 종양 중량을 비교함으로써 인간 폐암 A549 에 대한 siRNA 제형의 항종양 효능을 평가했다.

[0190] 동소이식 폐암 종양 억제를 구조 BU2 에 기반하는 GST- π siRNA (SEQ ID NO:1276 및 1341) 에 관해 생체내에서 관찰했다. 동소이식 A549 폐암 마우스 모델을 2 mg/kg 의 비교적 낮은 용량의 GST- π 를 표적으로 삼는 siRNA 와 함께 이용했다.

[0191] 이러한 6-주 연구에서 GST- π siRNA 는 유의미하고 예상외로 유리한 폐 종양 억제 효능을 보였다. 43 일 후에, GST- π siRNA 는 현저하게 유리한 종양 억제 효능을 보였으며, 최종 종양 평균 중량은 컨트롤과 비교할 때 2.8-배 만큼 유의미하게 감소했다.

[0192] 이러한 연구에서, 수컷 NCr nu/nu 마우스, 5-6 주령을 사용했다. 실험 동물을 실험 기간 동안 HEPA 여과되는 환경에서 유지했다. siRNA 제형을 사용 전에 4°C 에서 보관하고, 마우스에 주사하기 10 분 전에 실온으

로 가온했다.

- [0193] 이러한 A549 인간 폐암 동소이식 모델에 관해, 외과적 동소 이식 (SOI) 을 하는 날에, A549 종양 이중이식편을 보유하는 동물의 피하 부위로부터 스톡 종양을 수확하고 RPMI-1640 배지에 놓았다. 피사 조직을 제거하고, 생존가능한 조직을 1.5-2 mm 조각으로 잘랐다. 동물을 이소플루란 흡입으로 마취하고, 수술 부위를 요오드 및 알코올로 멸균했다. 한 쌍의 외과용 가위를 사용하여 마우스의 왼쪽 가슴 벽에 대략 1.5 cm 길이의 횡행 절개를 수행했다. 제 3 및 제 4 갈비뼈 사이에서 늑골간 절개를 수행했고, 왼쪽 폐를 노출시켰다. 하나의 A549 종양 단편을 8-0 외과용 봉합사 (나일론) 를 사용하여 폐의 표면에 이식했다. 가슴 벽을 6-0 외과용 봉합사 (실크) 로 닫았다. 25 G X 1 ½ 바늘을 갖는 3 cc 주사기를 사용하여 흉내 천자에 의해 폐를 재팽창시켜 흉강의 남은 공기를 빼냈다. 가슴 벽을 6-0 외과용 실크 봉합사로 닫았다. 위에 기재된 모든 수술 절차를 HEPA 여과되는 층류 후드 하에서 7 x 배율 현미경을 이용하여 수행했다.
- [0194] 종양 이식 후 3 일에, 모델 종양-보유 마우스를 그룹 당 10 마리 마우스의 그룹으로 무작위로 나누었다. 관심의 그룹에 관해, 10 마리 마우스의 처리를 종양 이식 후 3 일에 개시했다.
- [0195] 관심의 그룹에 관해, 제형은 (이온화가능 지질:콜레스테롤:DOPE:DOPC:DPPE-PEG-2K:DSPE-PEG-2K), 리포솜 조성물이었다. 리포솜은 GST- π siRNA 를 캡슐화했다.
- [0196] 연구 중점을 위해, 처리 개시 후 42 일에 실험 마우스를 희생시켰다. 후속의 분석을 위해 원발성 종양을 잘라내고 전자 밸런스에서 계량했다.
- [0197] 화합물 독성의 추정을 위해, 처리된 및 컨트롤 그룹 내 마우스의 평균 체중을 전체 실험 기간 동안 정상 범위 내에서 유지했다. 마우스에서 독성의 다른 증상이 관찰되지 않았다.
- [0198] **실시예 7:** 누드 마우스에서 A549 세포 성장에 대한 GST- π 를 표적하는 작은 간섭 RNA (siRNA) 의 효과 및 장요막 (CAM) 어세이에 대한 혈관신생. GST- π siRNA-플라스미드 및 비-침묵화-플라스미드의 3 개의 쌍을 제작하고, LIPOFECTAMINE 2000 을 통해 각각 A549 세포 내로 트랜스펙션했다. GST- π siRNA-플라스미드의 가장 효과적인 쌍을 ELISA 및 실시간 RT-PCR 에 의해 선별한다. A549 세포를 선별된 GST- π siRNA- 플라스미드로 트랜스펙션시키고, A549 세포를 비-침묵화-플라스미드로 트랜스펙션시키고, 트랜스펙션이 없는 A549 세포를 각각 누드 마우스 내로 접종한다. 병아리 배아를 무작위로 4 그룹으로 나누고, CAM 을 48 시간 동안 하기 상이한 용액으로 처리한다: 음성 컨트롤 그룹으로서 배양 배지 DMEM, 양성 컨트롤 그룹으로서 비-트랜스펙션된 A549 세포 배양 상청액, GST- π siRNA 그룹으로서 GST- π siRNA A549 세포 배양 상청액 및 비-침묵화 siRNA 그룹으로서 비-침묵화 siRNA A549 세포 배양 상청액. 현미경 어세이를 위해, CAM 을 제 12 일에 수확했다.
- [0199] 컨트롤 그룹과 비교하여, GST- π siRNA-플라스미드는 GST- π mRNA 에서 감소를 동반한 A549 세포에 의해 GST- π 분비에서의 감소를 유도한다. 비-침묵화 siRNA 그룹과 비교하여, 쫓과 이중이식의 평균 종양 체중은 GST- π siRNA 그룹에서 감소하고; 50 mm³ 까지 성장하는 이중이식에 대한 시간이 지연된다. 이중이식에서의 GST- π 함량은 감소된다. CAM 어세이에서, 음성 그룹에서 GST- π 함량은 0 이고, GST- π siRNA 그룹에서는 비-침묵화 siRNA 그룹 또는 양성 그룹과 비교하여 20-70% 감소한다; GST- π siRNA 그룹 또는 비-침묵화 siRNA 그룹 또는 양성 그룹에서의 CAM 의 혈관 분지점은 음성 그룹과 비교하여 증가된다; GST- π siRNA 그룹에서 CAM 의 총 혈관 길이는 음성 그룹과 비교하여 증가되는 반면, 비-침묵화 siRNA 그룹 또는 양성 그룹에서 이것은 증가된다. 음성 컨트롤 그룹과 비교하여, GST- π 가 있는 세포 배양 상청액을 GST- π siRNA 그룹에 첨가하는 경우 미세 혈관의 증식이 증가하고, 비-침묵화 siRNA 그룹 또는 양성 그룹에서 상당히 증식된 혈관이 관찰된다.
- [0200] **실시예 8:** 세포 배양. 인간 비-소형 세포 폐 암종 세포주, A549 를 5% CO₂ 의 가슴된 분위기 중의 37 °C 에서 10% FBS (FBS, Invitrogen) 가 보충된 F-12K 배지 (ATCC) 에서 배양한다. 컨트롤, 또는 GST π siRNA 를 안정하게 발현하는 세포는 제조자의 지침에 따라 (Sigma-Aldrich) A549TR 세포를 각각의 렌티바이러스 형질 도입 입자로 형질도입함으로써 발생시킨다. 저항성 클론을 2.5 μ g/mL 퓨로마이신 (Invivogen) 에서 12 d 동안 선별하고, 클로닝 원통을 사용하여 단리하고, 이어서 퓨로마이신-함유 배지에서 팽창 및 유지한다.
- [0201] **실시예 9:** GST- π 표적화 siRNA 는 생체 내에서 종양 부피의 엄청난 퇴행을 산출한다.
- [0202] 지질 제형은 scid 마우스에서 인간 A549 폐암 세포의 이중이식에 나노입자 중의 siRNA 를 캡슐화 및 전달하는데 사용된다. 정상 세포와 비교하여 KRAS 돌연변이의 존재 또는 이상 발현 수준을 확인하기 위해 이중이식을 시험한다. 종양이 성립되어 질 때 (>100 mm³), 마우스를 2 주 동안 매 2 일 GST- π 표적화 siRNA 또는 컨트롤

물 (비-특이적) siRNA 로 처리한다. 컨트롤 그룹을 안락사시켜야 할 때 시험을 중단한다.

[0203] 결과: GST- π 표적화 siRNA 로의 처리는 종양 팽창을 방지하고 현저한 종양 부피 감소를 산출한다.

[0204] 회수된 종양을 절개하고 TUNEL 염색에 의해 가시화한다. GST- π 표적화 siRNA-처리된 종양은 상당히 더 높은 수준의 세포자멸사를 나타낸다. 종양으로부터 RNA 를 추출하고, GST- π 의 특이적 녹다운을 시험하기 위해 실시간 PCR 을 수행한다.

[0205] 결과: GST- π 표적화 siRNA 로의 처리는 생체 내 GST- π 의 발현을 현저히 감소시킨다.

[0206] **실시예 10:** 본 발명의 GST- π siRNA 는 증가된 혈청 안정성을 나타냈다.

[0207] GST- π siRNA 를 인간 혈청 중 인큐베이션하고 HPLS/LCMS 에 의한 다양한 시점에서의 남은 siRNA 의 검출을 수행했다. GST- π siRNA (SEQ ID No:1276 및 1341) 의 센스 가닥 및 안티센스 가닥 둘 모두에 관한 혈청 중 반감기 ($t_{1/2}$) 는 약 100 분이었다.

[0208] **실시예 11:** 본 발명의 GST- π siRNA 는 혈장 중 제형에서 향상된 안정성을 나타냈다.

[0209] GST- π siRNA 를 혈장 중 제형에서 인큐베이션하고 다양한 시점에서의 남은 siRNA 의 검출을 수행했다. GST- π siRNA (SEQ ID NO:1276 및 1341) 의 제형의 혈장 중 반감기 ($t_{1/2}$) 는 100 시간 보다 유의미하게 더 길었다.

[0210] GST- π siRNA 를 조성 (이온화 지질: 콜레스테롤: DOPE: DOPC: DPPE-PEG-2K) (25:30:20:20:5) 을 갖는 리포솜 제형으로 제조했다. 리포솜 나노입자에 관한 z-평균 크기는 40.0 nm 였고, siRNA 는 91% 캡슐화되었다.

[0211] 제형을 PBS 중 50% 인간 혈청 중 40min, 1.5h, 3h, 24h, 및 96h 동안 인큐베이션했다. GST- π siRNA 의 양을 ELISA-기반 검정에 의해 확인했다.

[0212] **실시예 12:** 본 발명의 GST- π siRNA 는 생체내에서 암 이종이식 종양의 현저한 감소를 나타낼 수 있다. GST- π siRNA 는 생체내에서 리포솜 제형으로 암 이종이식 종양에 투여될 때 유전자 녹다운 효력을 제공할 수 있다.

[0213] GST- π siRNA (SEQ ID NO:1276 및 1341) 에 관한 종양 억제 효능이 관찰되었다. GST- π 를 표적으로 삼는 siRNA 로 생체내에서 GST- π mRNA 의 용량 의존적 녹다운이 관찰되었다. 암 이종이식 모델을 GST- π 를 표적으로 삼는 siRNA 와 함께 이용했다.

[0214] GST- π siRNA 는 투여 후 수일 내에 유의미하고 예상외로 유리한 종양 억제 효능을 보였다. GST- π siRNA 에 의한 처리는 지질 제형 중 주사 후 4 일에 GST- π mRNA 발현의 유의미한 감소를 초래했다. 4 mg/kg 의 더 높은 용량에서, 주사 후 24 시간에 약 40% 의 유의미한 감소가 검출되었다.

[0215] GST- π siRNA 를 조성 (이온화가능 지질: 콜레스테롤: DOPE: DOPC: DPPE-PEG-2K) (25:30:20:20:5) 을 갖는 리포솜 제형의 10 mL/kg 의 단일 주사로 투여했다.

[0216] 암 이종이식 모델에 관해, A549 세포주를 ATCC로부터 수득했다. 세포를 10% 우태 혈청 및 100 U/mL 페니실린 및 100 μ g/mL 스트렙토마이신으로 보강된 RPMI-1640 에서 유지했다. 세포를 접종 전 48 시간에 분할하여 세포가 수확될 때 로그기 성장에 있게 했다. 세포를 트립신-EDTA 로 약간 트립신화하고, 조직 배양물로부터 수확했다. 생존 세포의 수를 트립판 블루의 존재 하에 혈구계에서 카운트 및 확인했다 (오직 생존 세포를 카운트한다). 세포를 혈청 없는 RPMI 배지에 4×10^7 /mL 의 농도로 재현탁시켰다. 그 후 세포 현탁액을 주사를 위해 얼음 해동된 BD 매트릭셀과 1:1 비로 잘 혼합했다.

[0217] 마우스는 Charles River Laboratory 무흉선 누드 (nu/nu) 암컷 마우스 (면역-약화된, 6-8 주령, 그룹 당 3 마리의 마우스) 였다.

[0218] 종양 모델 제조를 위해, 각 마우스에 25 G 바늘 및 주사기를 사용하여 2×10^6 개 A549 세포의 0.1 mL 접종물을, 마우스 당 하나의 접종물을 오른쪽 옆구리에 피하 접종했다. 마우스를 접종을 위해 마취하지 않았다.

[0219] 종양 부피 측정 및 무작위화를 위해, 종양 크기를 0.1 mm 가까이로 측정했다. 종양 부피를 다음 식을 사용하여 계산했다: 종양 부피 = 길이 x 너비²/2. 종양 부피를 1 주 2 회 모니터링했다. 확립된 종양이 대략 350 - 600 mm³ 에 도달했을 때, 마우스를 다양한 시점에서 그룹에 배정했다. 동일한 날에, 시험품을 투약

레지멘에 따라 투여했다.

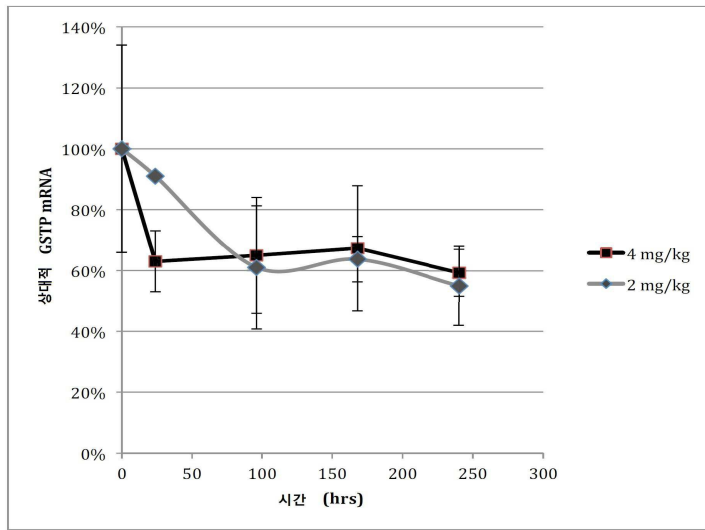
- [0220] 투여량 투여를 위해, 확립된 종양이 대략 350 - 600 mm³에 도달한 날에, 시험품을 4℃ 냉장고에서 꺼냈다. 주사기에 넣기 전에, 제형을 함유하는 병을 손으로 몇 번 뒤집어서 균질한 용액을 만들었다.
- [0221] 체중에 관해, 마우스를 0.1 g 가까이로 계량했다. 체중을 몇 주 동안, 연구 종료일을 포함하여, 나머지 주 동안 2 회 모니터링 및 기록했다.
- [0222] 종양 수집을 위해, 동물을 과다투여된 CO₂에 의해 희생시키고, 종양을 투약 후 0, 24, 48, 72, 96 (선택적), 및 168 시간에 해부했다. 종양을 먼저 습윤 계량하고, 그 후 KD, 분포 및 바이오마커 분석을 위해 3 개의 부분으로 분리했다. 샘플을 액체 질소 중에 급속 냉동시키고, 가공될 준비가 될 때까지 -80 °C에서 보관했다.
- [0223] 본원에서 기재된 구현에는 제한적이지 않고, 당업자는 개선된 RNAi 활성을 갖는 핵산 분자를 식별하기 위해 과도한 실험과정 없이 본원에서 기재된 변형예의 특정 조합이 시험될 수 있다는 것을 쉽게 인지할 수 있다.
- [0224] 본원에서 구체적으로 언급된 모든 공보, 특허 및 문헌은 그 전체가 모든 목적을 위해 참고로 편입된다.
- [0225] 본 발명은 기재된 특정 방법론, 프로토콜, 물질, 및 시약에 제한되지 않으며, 이들은 달라질 수 있다. 또한 본원에서 사용된 용어는 오직 특정한 구현예를 설명하기 위한 것으로 이해될 것이고, 본 발명의 범위를 제한하는 것이 의도되지 않는다. 설명의 범위 및 주제에서 벗어나지 않으면서 본원에서 개시된 설명에 다양한 치환 및 개질이 만들어질 수 있고, 이들 구현예는 이러한 설명 및 첨부된 청구항들의 범위 내에 있다는 것이 당업자에게 쉽게 명백할 것이다.
- [0226] 본 명세서에서 및 첨부된 청구항들에서 사용된 바와 같이, 단수 형태 "하나", "하나의", 및 "그러한"은 문맥이 명백히 다르게 언급하지 않으면 복수의 언급 대상을 포함한다는 점에 주의해야 한다. 또한, 용어들 "하나" (또는 "하나의"), "하나 이상의" 및 "적어도 하나"는 본원에서 상호교환적으로 사용될 수 있다. 용어들 "포함한다," "포함하는," "함유하는," "포함되어", 및 "갖는"은 상호교환적으로 사용될 수 있고, 확장적으로 및 비제한적으로 이해되어야 한다는 점에 또한 주의해야 한다.
- [0227] 본원에서 값의 범위의 언급은, 본원에서 달리 명시되지 않는 한, 단지 범위 내에 있는 각 별개의 값을 개별적으로 언급하는 속기 방법으로서의 역할을 하는 것으로 의도되고, 각 별개의 값은 마치 그것이 본원에서 개별적으로 인용된 것처럼 명세서에 편입된다. 마쿠쉬 그룹에 관해, 당업자는 이러한 설명이 개별적인 구성원, 뿐만 아니라 마쿠쉬 그룹의 구성원의 하위기를 포함한다는 것을 이해할 것이다.
- [0228] 추가의 상세한 설명 없이, 당업자는, 상기 설명에 기반하여, 본 발명을 그것의 최대한의 정도까지 이용할 수 있다고 여겨진다. 하기 특정 구현예는, 따라서, 단지 예시적으로 해석될 것이고, 공개의 나머지를 어떤 식으로든 제한하지 않는다.
- [0229] 본 명세서에 개시된 모든 특징은 임의의 조합으로 조합될 수 있다. 본 명세서에 개시된 각 특색은 동일한, 대등한, 또는 유사한 목적에 기여하는 대안적인 특색으로 대체될 수 있다.

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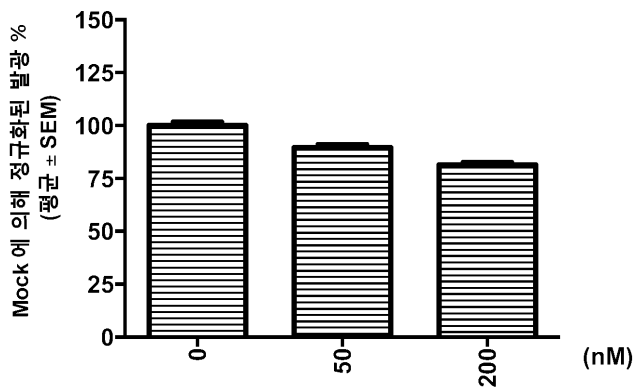
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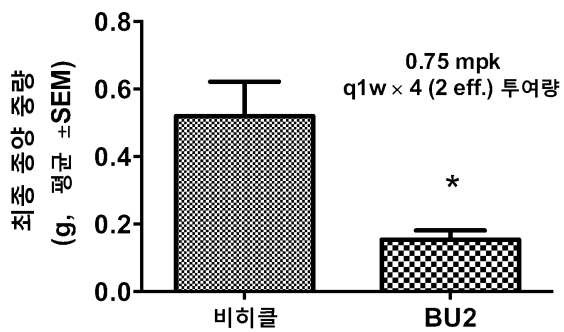
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도면3



도면4



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<210> 1070

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<210> 1087

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<400> 1253

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<210> 1301

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<210> 1306

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21