INFORME TECNOLÓGICO DE PATENTES

DEPARTAMENTO DE PATENTES E INFORMACIÓN TECNOLÓGICA

SERVICIO DE BÚSQUEDAS

DEPARTAMENTO DE PATENTES E INFORMACIÓN TECNOLÓGICA. SERVICIO DE BÚSQUEDAS
Paseo de la Castellana, 75 - 28071 MADRID (ESPAÑA). Tel.: 902.157.530. FAX: 91-457-25-86. http://www.oepm.es

✓ **NÚMERO DE ORDEN:** V1135

✓ **FECHA:** 2 de enero de 2013

✓ **SOLICITANTE:** XXXXXX

✓ **TÍTULO:** Uso de ARN de interferencia en el tratamiento de la enfermedad de Huntington

✓ **RESPONSABLE:** XXXXXX

✓ **PERFIL DE BÚSQUEDA**

- Clasificación Internacional de Patentes

C12N 15/09· Tecnología del ADN recombinante
C12N 15/11· · Fragmentos de ADN o de ARN; sus formas modificadas
C12N 15/113· · · Acidos nucleicos no codificantes que modulan la expresión de genes, p.ej. oligonucleótidos antisentido

A61K48/00: Preparaciones medicinales que contienen material genético que se introduce en las céluas del cuerpo; Terapia génica

- Clasificación Cooperativa de Patentes

C12N15/113: Non-coding nucleic acids modulating the expression of genes, e.g.antisense oligonucleotides; [N: Antisense DNA or RNA; Triplex- forming oligonucleotides; Catalytic nucleic acids, e.g. ribozymes; Nucleic acids used in co-suppression or gene silencing

C12N2310/14: Structure or type of the nucleic acid; Interfering N.A.

- Palabras Clave

En INVENES: Huntington, huntintina, HTT, ARN, ARNip, siARN, iARN, ARNic, interferencia, silenciamiento, alelo

En Bases Externas: Huntington, huntingtin, HTT, RNA, iRNA, siRNA, interfering, silence, silencing, allele

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Resultado de la búsqueda

1. DOCUMENTOS ESPECIALMENTE RELACIONADOS CON EL OBJETO DE BÚSQUEDA

En este apartado se incluyen todos los documentos que se han considerado más próximos al perfil de búsqueda solicitado, seleccionados de entre todos los analizados.

- **Modelos de utilidad españoles, patentes españolas y solicitudes de patentes europeas y solicitudes PCT que designan España.**

  WO2012144906 (PROSENSA TECHNOLOGIES B V) 26.10.2012
  WO2010118263 (UNIV MASSACHUSETTS) 14.10.2010

- **Patentes extranjeras.**

  US2011213010 (UNIV BRITISH COLUMBIA) 01.09.2011

- **Publicaciones científicas**

  Hu Jiaxin, et al. Allele-specific silencing of mutant huntingtin and ataxin-3 genes by targeting expanded CAG repeats in mRNAs. Nature biotechnology, May 2009, vol 27(5), pp. 478-484. ISSN 1546-1696 (Electronic). Accesible gratuitamente en: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2765218/pdf/nihms107907.pdf

  Pfister Edith l. et al. Five siRNAs targeting three SNPs may provide therapy for three-quarters of Huntington's disease patients. Current Biology, 12.05.2009, vol. 19(9), pp. 774-778. doi:10.1016/j.cub.2009.03.030.
  http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2746439/pdf/nihms118144.pdf

2. OTROS DOCUMENTOS DE INTERÉS

Incluidos en el Anexo 1 estos documentos reflejan el estado de la técnica en relación al objeto de búsqueda. Las referencias bibliográficas recuperadas incluyen un hipervínculo que permite el acceso al documento completo a través de las bases de datos de patentes INVENES y esp@cenet.

El texto completo de los documentos japoneses posteriores a 1993 puede obtenerse en inglés directamente de la página Web de la Oficina de Patentes Japonesa, dentro de la Biblioteca Digital de Propiedad Industrial (IPDL) activando el correspondiente traductor automático. Basta con introducir en la base de datos PAJ (Patent Abstracts of Japan) el número de publicación del documento deseado y activar el botón una vez que se ha obtenido su correspondiente referencia bibliográfica en inglés. http://www19.ipdl.inpit.go.jp/PA1/cgi-bin/PA1INIT.

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COMENTARIO

La finalidad del presente informe es la recuperación de información tanto de patentes como de literatura no patente sobre el uso de ARNs interferentes de pequeño tamaño (siRNA) para el silenciamiento de genes relacionados con la enfermedad de Huntington, con vistas a la patentabilidad de una invención basada en esta tecnología. Concretamente, el proyecto objeto del presente informe se basa en el uso de conjugados siRNA-oligopéptido.

Como punto de partida se ha utilizado la memoria técnica aportada por el solicitante en la que se realiza una somera descripción del estado de la técnica, se proponen una serie de palabras clave en relación con la invención y se aportan las secuencias de 3 conjugados ensayados. Dicha memoria no incluye un borrador de reivindicaciones de una posible solicitud de patente.

La búsqueda documental se ha realizado utilizando bases de datos de patentes de cobertura internacional (WPI; EPODOC) y bases de datos de literatura científica, todas ellas accesibles a través del sistema EPOQUE de la Oficina Europea de Patentes (BIOSIS, MEDLINE, EMBASE, NPL, XPESP) (Ver anexos 2 y 3 para más información). También se ha consultado la base de datos de patentes en España INVENES. Para la búsqueda de secuencias se ha utilizado el entorno de búsqueda del EBI (European Bioinformatics Institute) a través de una línea segura.

Con la estrategia de búsqueda empleada se han recuperado más de 100 documentos. De todos ellos se ha consultado el título y el resumen y, los considerados más relevantes, se han analizado en profundidad.

Como primera consecuencia del análisis de los documentos recuperados, se aprecia que ya está descrito el uso de siRNA en el tratamiento de enfermedades neurodegenerativas (ver por ejemplo ES2352630 y ES2352925 en el listado de referencias de la base de datos INVENES) y más concretamente en la terapia de la enfermedad de Huntington (ver ES2334125 en el mismo listado que las anteriores). Por lo que se refiere al segundo y más concreto aspecto de la invención relativo al uso de conjugados siRNA-oligopéptido, se han considerado próximos al objeto de la búsqueda dos solicitudes internacionales PCT y una estadounidense:

WO2012144906 (PROSENSA TECHNOLOGIES B V): divulga oligonucleotidos modificados que son útiles para el tratamiento de enfermedades debidas a expansiones del triplete GAC. Preferentemente los oligonucleótidos a los que se refiere son ARNs pequeños de cadena sencilla que llevan unido un péptido corto de secuencia Leu-Gly-Ala-Gln-Ser-Asn-Phe que facilita su entrada en la célula.

WO2010118263 (UNIV MASSACHUSETTS): describe un kit que contiene una serie de ARNs de interferencia cada uno específico para silenciar un SNP relacionado con una mutación concreta en el gen de la huntingtina. En una de las formas de realización se divulgan ARNs de interferencia unidos a diversos ligandos entre los que se encuentran péptidos cortos o peptidomiméticos que protegen a los ácidos nucleicos de la degradación por acción de las nucleasas.

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US2011213010 (UNIV BRITISH COLUMBIA): se refiere a composiciones para reducir la expresión de la huntigtina mutante en una célula. Están basadas en ácidos nucleicos silenciadores específicos del polimorfismo en el ARN que codifica dicha proteína que van unidos a un vehículo que puede ser un péptido corto de naturaleza catiónica.

Con respecto a la búsqueda en bases de datos de literatura científica, los resultados son similares a los comentados en el párrafo anterior (ver listados de referencias de los anexos 1A y 1B). Se han seleccionado dos publicaciones particularmente relacionadas con la invención:

Hu Jiaxin, et al. : artículo que divulga oligonucleótidos antisentido y conjugados ácido nucleico-péptido de diferentes longitudes que, dirigidos a las repeticiones CAG, son capaces de distinguir el gen mutante en función de la longitud de las repeticiones y en consecuencia inhibir la expresión de la huntingtina mutante de forma más selectiva que los ARNs pequeños de doble cadena (ver documento completo en el enlace que se facilita).

Pfister Edith l. et al.: publicación en la que los autores secuencian 22 SNPs en muestras procedentes de individuos sanos y enfermos, identifican 3 de ellos relacionados con la enfermedad de Huntington y diseñan y validan 5 siRNAs que serían efectivos para el silenciamiento aleloespecífico de la mayor parte de los afectados por la enfermedad en Europa y EE.UU (ver documento completo en el enlace que se facilita).

En vista de todo lo anterior, cabría concluir que existen publicaciones que divulgan los conjugados péptido-siRNA en el silenciamiento de la expresión de las repeticiones CAG en el gen de la huntingtina y por lo tanto podrían ser efectivos en el tratamiento de la enfermedad de Huntington. También están descritas construcciones que son capaces de distinguir numerosos polimorfismos y SNPs relacionados con la enfermedad de Huntington. Sin embargo, dado que ninguno de los documentos recuperados divulga las secuencias de la invención, los conjugados objeto del presente informe se considerarían nuevos.

No obstante, dado que se trata de una tecnología conocida, con el fin de reforzar la actividad inventiva de una posible solicitud de patente, sería conveniente que esta aportara argumentos que permitieran confirmar inequívocamente que la naturaleza de los conjugados a que se refiere la memoria técnica es determinante a la hora de superar las limitaciones de estabilidad y biodisponibilidad que encuentran *in vivo* las moléculas de ARN de interferencia cuando se administran de forma exógena.

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Se adjuntan los siguientes Anexos:

ANEXO 1. Listado de referencias

A) Base de Datos BIOSIS

B) Base de Datos MEDLINE

C) Base de Datos WPI

D) Base de Datos INVENES

ANEXO 2. Bases de datos utilizadas.

ANEXO 3. Códigos de las bases de datos.

ANEXO 4. Abreviaturas de países.

ANEXO 5. Glosario de términos de propiedad industrial.

*NOTA: El presente Informe se ha realizado con el máximo rigor, de acuerdo con una metodología consolidada y tratando de ceñirse estrechamente a las necesidades del solicitante. Este Informe **no vincula** a la OEPM en lo que se refiere a los resultados que puedan obtenerse de una subsiguiente solicitud formal de registro en alguna de las modalidades de propiedad industrial*

Le informamos que puede obtener deducciones fiscales por actividades de investigación, desarrollo e innovación tecnológica. En caso de que el objeto de su proyecto se corresponda con el de un Informe Tecnológico de Patentes (ITP) realizado por la OEPM, podrá aportarlo a la entidad certificadora acreditada por ENAC para la realización de informes técnicos relacionados con los informes motivados vinculantes que establece el Real Decreto 1432/2003 de 21 de noviembre, teniendo esta el compromiso de realizarle un descuento fijo equivalente al 50% del precio del Informe Tecnológico de Patentes. (Convenio de colaboración suscrito entre el Ministerio de Ciencia e Innovación, la Oficina Española de Patentes y Marcas y las Entidades certificadoras) Más información

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ANEXO 1. Listado de referencias

A) Base de Datos BIOSIS

1/3 - (C) BIOSIS / BIOSIS
AN - PREV200900353919
TI - Five siRNAs Targeting Three SNPs May Provide Therapy for Three-Quarters of Huntington's Disease Patients
AU - Pfister Edith L; Kennington Lori; Straubhaar Juerg; Wagh Sujata; Liu Wanzhou; DiFiglia Marian; Landwehrmeyer Bernhard; Vonsattel Jean-Paul; Zamore Phillip D; Aronin Neil
AUAF- Univ Massachusetts, Sch Med, Howard Hughes Med Inst, Dept Biochem and Mol Biol, Worcester, MA 01605 USA; phillip.zamore@umassmed.edu, neil.aronin@umassmed.edu
PUB - Current Biology
- MAY 12 2009
LNKD- doi:10.1016/j.cub.2009.03.030
IRN - ISSN 0960-9822
VOL - 19
NR - 9
PG - 774-778
AB - Among dominant neurodegenerative disorders, Huntington's disease (HD) is perhaps the best candidate for treatment with small interfering RNAs (siRNAs) [1-9]. Invariably fatal, HD is caused by expansion of a CAG repeat in the Huntingtin gene, creating an extended polyglutamine tract that makes the Huntingtin protein toxic [10]. Silencing mutant Huntingtin messenger RNA (mRNA) should provide therapeutic benefit, but normal Huntingtin likely contributes to neuronal function [11-13]. No si RNA strategy can yet distinguish among the normal and disease Huntingtin alleles and other mRNAs containing CAG repeats [14]. siRNAs targeting the disease isoform of a heterozygous single-nucleotide polymorphism (SNP) in Huntingtin provide an alternative [15-19]. We sequenced 22 predicted SNP sites in 225 human samples corresponding to HD and control subjects. We find that 48% of our patient population is heterozygous at a single SNP site; one isoform of this SNP is associated with HD. Several other SNP sites are frequently heterozygous. Consequently, five allele-specific siRNAs, corresponding to just three SNP sites, could be used to treat three-quarters of the United States and European HD patient populations. We have designed and validated selective siRNAs for the three SNP sites, laying the foundation for allele-specific RNA interference (RNAi) therapy for HD.

2/3 - (C) BIOSIS / BIOSIS
AN - PREV200800476657
TI - Identification and allele-specific silencing of the mutant huntingtin allele in Huntington's disease patient-derived fibroblasts
AU - van Bilsen P H J; Jaspers L; Lombardi M S; Odekerken J C E; Burright E N; Kaemmerer W F
AUAF- Medtron World Headquarters, Sci and Technol Corp, 710 Medtron Pkwy NE, Minneapolis, MN 55432 USA; bill.kaemmerer@medtronic.com
PUB - Human Gene Therapy
- JUL 2008
LNKD- doi:10.1089/hum.2007.116
IRN - ISSN 1043-0342
VOL - 19
NR - 7

PG - 710-718
AB - Huntington's disease (HD) is a dominantly inherited neurodegenerative disorder caused by the expression of mutant huntingtin protein (Htt). Suppression of Htt expression, using RNA interference, might be an effective therapy. However, if reduction of wild-type protein is not well tolerated in the brain, it may be necessary to suppress just the product of the mutant allele. We present a small interfering RNA (siRNA) that selectively reduces the endogenous mRNA for a heterozygous HD donor's pathogenic allele by approximately 80% by specifically targeting a single-nucleotide polymorphism (SNP) located several thousand bases downstream from the disease-causing mutation. In addition, we show selective suppression of endogenous mutant Htt protein, using this siRNA. We further present a method, using just a heterozygous patient's own mRNA, to determine which SNP variants correspond to the mutant allele. The method may be useful in any disorder in which a targeted SNP is far downstream from the pathogenic mutation. These results indicate that allele-specific treatment for Huntington's disease may be clinically feasible and practical.

3/3 - (C) BIOSIS / BIOSIS
AN - PREV200300192613
TI - Suppression of huntingtin gene expression by siRNA: A possible therapeutic tool for Huntington's disease.
AU - Goto Jun; Liu Wanzhao; Murata Miho; Nemoto Naoto; Kanazawa Ichiro
AUAF- Bunkyo-ku, Tokyo, Japan
PUB - Neurology
- March 11, 2003
IRN - ISSN 0028-3878 (ISSN print)
VOL - 60
NR - 5 Supplement 1
PG - A286
CONF- 55th Annual Meeting of the American Academy of Neurology; Honolulu, Hawaii, USA; March 29-April 05, 2003

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B) Base de Datos MEDLINE

1/11 - (C) MEDLINE / NLM
AN - NLM19796074
DT - Journal Article, Research Support, N.I.H., Extramural, Research Support, Non-U.S. Gov't
TI - Allele-selective inhibition of mutant huntingtin by peptide nucleic acid-peptide conjugates, locked nucleic acid, and small interfering RNA.
AU - Hu Jiaxin; Matsui Masayuki; Corey David R
PUB - Annals of the New York Academy of Sciences
- United States
- Sep 2009
ORD - 2009-09-00
LNKD- pubmed:19796074
IRN - ISSN 1749-6632 (Electronic)
VOL - 1175
PG - 24 - 31
LA - eng
IW - Alleles; Humans; Huntington Disease: therapy(#); Nerve Tissue Proteins: antagonists & inhibitors(#), genetics; Nuclear Proteins: antagonists & inhibitors(#), genetics; Oligonucleotides: chemistry, genetics(#), therapeutic use; Peptide Nucleic Acids: chemistry, genetics(#), therapeutic use; RNA, Small Interfering: chemistry, genetics(#), therapeutic use; Selection, Genetic
AW - HTT protein, human; Nerve Tissue Proteins; Nuclear Proteins; Oligonucleotides; Peptide Nucleic Acids; RNA, Small Interfering; locked nucleic acid
AB - The ability to inhibit expression of a mutant allele while retaining expression of a wild-type protein might provide a useful approach to treating Huntington's Disease (HD) and other inherited pathologies. The mutant form of huntingtin (HTT), the protein responsible for HD, is encoded by an mRNA containing an expanded CAG repeat. We demonstrate that peptide nucleic acid conjugates and locked nucleic acids complementary to the CAG repeat selectively block expression of mutant HTT. The selectivity of inhibition is at least as good as that shown by a small interfering RNA targeted to a deletion polymorphism. Our data suggest that antisense oligomers are promising subjects for further development as an anti-HD therapeutic strategy.

2/11 - (C) MEDLINE / NLM
AN - NLM19289118
DT - Journal Article
TI - A majority of Huntington's disease patients may be treatable by individualized allele-specific RNA interference.
AU - Lombardi Maria Stella; Jaspers Leonie; Spronkmans Christine; Gellera Cinzia; Taroni Franco; Di Maria Emilio; Donato Stefano Di; Kaemmerer William F
PUB - Experimental neurology
- United States
- Jun 2009
ORD - 2009-03-13
LNKD- pubmed:19289118
IRN - ISSN 1090-2430 (Electronic)
VOL - 217
NR - 2

PG - 312 - 319
LA - eng
IW - Adolescent; Adult; Aged; Aged, 80 and over; Alleles(#); Child; Cohort Studies; DNA Mutational Analysis; Female; Gene Frequency; Gene Targeting: methods; Gene Therapy: methods(#); Genetic Testing; Heterozygote; Humans; Huntington Disease: genetics, physiopathology, therapy(#); Male; Middle Aged; Polymorphism, Single Nucleotide: genetics; RNA Interference: physiology(#); RNA, Small Interfering: therapeutic use; Young Adult
AW - RNA, Small Interfering
AB - Use of RNA interference to reduce huntingtin protein (htt) expression in affected brain regions may provide an effective treatment for Huntington disease (HD), but it remains uncertain whether suppression of both wild-type and mutant alleles in a heterozygous patient will provide more benefit than harm. Previous research has shown suppression of just the mutant allele is achievable using siRNA targeted to regions of HD mRNA containing single nucleotide polymorphisms (SNPs). To determine whether more than a minority of patients may be eligible for an allele-specific therapy, we genotyped DNA from 327 unrelated European Caucasian HD patients at 26 SNP sites in the HD gene. Over 86% of the patients were found to be heterozygous for at least one SNP among those tested. Because the sites are genetically linked, one cannot use the heterozygosity rates of the individual SNPs to predict how many sites (and corresponding allele-specific siRNA) would be needed to provide at least one treatment possibility for this percentage of patients. By computing all combinations, we found that a repertoire of allele-specific siRNA corresponding to seven sites can provide at least one allele-specific siRNA treatment option for 85.6% of our sample. Moreover, we provide evidence that allele-specific siRNA targeting these sites are readily identifiable using a high throughput screening method, and that allele-specific siRNA identified using this method indeed show selective suppression of endogenous mutant htt protein in fibroblast cells from HD patients. Therefore, allele-specific siRNA are not so rare as to be impractical to find and use therapeutically.

3/11 - (C) MEDLINE / NLM
AN - NLM19412185
DT - Journal Article, Research Support, N.I.H., Extramural, Research Support, Non-U.S. Gov't
TI - Allele-specific silencing of mutant huntingtin and ataxin-3 genes by targeting expanded CAG repeats in mRNAs.
AU - Hu Jiaxin; Matsui Masayuki; Gagnon Keith T; Schwartz Jacob C; Gabillet Sylvie; Arar Khalil; Wu Jun; Bezprozvanny Ilya; Corey David R
PUB - Nature biotechnology
- United States
- May 2009
ORD - 2009-05-00
LNKD- pubmed:19412185
IRN - ISSN 1546-1696 (Electronic)
VOL - 27
NR - 5
PG - 478 - 484
LA - eng
IW - Animals; Cell Line; Cells, Cultured; Female; Fibroblasts: metabolism; Humans; Huntington Disease: genetics(#); Machado-Joseph Disease: genetics; Male; Mice; Nerve Tissue Proteins: genetics(#); Nuclear Proteins: genetics(#); Oligonucleotides, Antisense: metabolism(#);

Peptide Nucleic Acids: metabolism(#); Repressor Proteins: genetics(#); Trinucleotide Repeat Expansion(#)
AW - HTT protein, human; Nerve Tissue Proteins; Nuclear Proteins; Oligonucleotides, Antisense; Peptide Nucleic Acids; Repressor Proteins; ATXN3 protein, human
AB - Expanded trinucleotide repeats cause many neurological diseases. These include Machado-Joseph disease (MJD) and Huntington's disease (HD), which are caused by expanded CAG repeats within an allele of the ataxin-3 (ATXN3) and huntingtin (HTT) genes, respectively. Silencing expression of these genes is a promising therapeutic strategy, but indiscriminate inhibition of both the mutant and wild-type alleles may lead to toxicity, and allele-specific approaches have required polymorphisms that differ among individuals. We report that peptide nucleic acid and locked nucleic acid antisense oligomers that target CAG repeats can preferentially inhibit mutant ataxin-3 and HTT protein expression in cultured cells. Duplex RNAs were less selective than single-stranded oligomers. The activity of the peptide nucleic acids does not involve inhibition of transcription, and differences in mRNA secondary structure or the number of oligomer binding sites may be important. Antisense oligomers that discriminate between wild-type and mutant genes on the basis of repeat length may offer new options for developing treatments for MJD, HD and related hereditary diseases.

4/11 - (C) MEDLINE / NLM
AN - NLM17940007
DT - Journal Article, Research Support, N.I.H., Extramural, Research Support, Non-U.S. Gov't
TI - Therapeutic silencing of mutant huntingtin with siRNA attenuates striatal and cortical neuropathology and behavioral deficits.
AU - DiFiglia M; Sena-Esteves M; Chase K; Sapp E; Pfister E; Sass M; Yoder J; Reeves P; Pandey R K; Rajeev K G; Manoharan M; Sah D W Y; Zamore P D; Aronin N
PUB - Proceedings of the National Academy of Sciences of the United States of America
- United States
- 23 Oct 2007
ORD - 2007-10-16
LNKD- pubmed:17940007
IRN - ISSN 0027-8424 (Print)
VOL - 104
NR - 43
PG - 17204 - 17209
LA - eng
IW - Animals; Behavior, Animal: drug effects; Cerebral Cortex: drug effects, pathology(#); Cholesterol: metabolism; Dependovirus; Disease Models, Animal; Gene Silencing(#); Gene Therapy(#); Humans; Huntington Disease: pathology, therapy; Injections; Intranuclear Inclusion Bodies: drug effects, pathology, ultrastructure; Mice; Motor Neuron Disease: pathology; Mutant Proteins: antagonists & inhibitors(#); Neostriatum: drug effects, pathology(#); Nerve Tissue Proteins: antagonists & inhibitors(#), immunology; Neurons: pathology, ultrastructure; Neuropil Threads: drug effects, ultrastructure; Nuclear Proteins: antagonists & inhibitors(#), immunology; RNA, Small Interfering: pharmacology(#)
AW - HTT protein, human; Mutant Proteins; Nerve Tissue Proteins; Nuclear Proteins; RNA, Small Interfering; Cholesterol
AB - Huntington's disease (HD) is a neurodegenerative disorder caused by expansion of a CAG repeat in the huntingtin (Htt) gene. HD is

autosomal dominant and, in theory, amenable to therapeutic RNA silencing. We introduced cholesterol-conjugated small interfering RNA duplexes (cc-siRNA) targeting human Htt mRNA (siRNA-Htt) into mouse striata that also received adeno-associated virus containing either expanded (100 CAG) or wild-type (18 CAG) Htt cDNA encoding huntingtin (Htt) 1-400. Adeno-associated virus delivery to striatum and overlying cortex of the mutant Htt gene, but not the wild type, produced neuropathology and motor deficits. Treatment with cc-siRNA-Htt in mice with mutant Htt prolonged survival of striatal neurons, reduced neuropil aggregates, diminished inclusion size, and lowered the frequency of clasping and footslips on balance beam. cc-siRNA-Htt was designed to target human wild-type and mutant Htt and decreased levels of both in the striatum. Our findings indicate that a single administration into the adult striatum of an siRNA targeting Htt can silence mutant Htt, attenuate neuronal pathology, and delay the abnormal behavioral phenotype observed in a rapid-onset, viral transgenic mouse model of HD.

5/11 - (C) MEDLINE / NLM
AN - NLM16095740
DT - Journal Article, Research Support, Non-U.S. Gov't
TI - Clinico-pathological rescue of a model mouse of Huntington's disease by siRNA.
AU - Wang Yu-Lai; Liu Wanzhao; Wada Etsuko; Murata Miho; Wada Keiji; Kanazawa Ichiro
PUB - Neuroscience research
- Ireland
- Nov 2005
ORD - 2005-08-10
LNKD- pubmed:16095740
IRN - ISSN 0168-0102 (Print)
VOL - 53
NR - 3
PG - 241 - 249
LA - eng
IW - Animals; Body Weight: genetics; Corpus Striatum: metabolism, pathology, physiopathology; Disease Models, Animal; Female; Gene Expression Regulation: drug effects, genetics; Gene Therapy: methods(#); Humans; Huntington Disease: genetics(#), physiopathology, therapy(#); Injections, Intraventricular; Intranuclear Inclusion Bodies: genetics, metabolism, pathology; Male; Mice; Mice, Transgenic; Motor Activity: genetics; Nerve Tissue Proteins: biosynthesis, genetics(#); Nuclear Proteins: biosynthesis, genetics(#); Peptides: genetics, metabolism; RNA, Small Interfering: genetics, therapeutic use(#); Survival Rate; Transgenes: genetics; Treatment Outcome; Trinucleotide Repeat Expansion: genetics
AW - HTT protein, human; Nerve Tissue Proteins; Nuclear Proteins; Peptides; RNA, Small Interfering; polyglutamine
AB - Huntington's disease (HD) is an autosomal dominant inheritable neurodegenerative disorder currently without effective treatment. It is caused by an expanded polyglutamine (poly Q) tract in the corresponding protein, huntingtin (htt), and therefore suppressing the huntingtin expression in brain neurons is expected to delay the onset and mitigate the severity of the disease. Here, we have used small interfering RNAs (siRNAs) directed against the huntingtin gene to repress the transgenic mutant huntingtin expression in an HD mouse model, R6/2. Results showed that intraventricular injection of siRNAs at an early postnatal period inhibited transgenic huntingtin

expression in brain neurons and induced a decrease in the numbers and sizes of intranuclear inclusions in striatal neurons. Treatments using this siRNA significantly prolonged model mice longevity, improved motor function and slowed down the loss of body weight. This work suggests that siRNA-based therapy is promising as a future treatment for HD.

6/11 - (C) MEDLINE / NLM
AN - NLM16237462
DT - Journal Article, Research Support, N.I.H., Extramural, Review
TI - RNAi: a potential therapy for the dominantly inherited nucleotide repeat diseases.
AU - Denovan-Wright E M; Davidson B L
PUB - Gene therapy
- England
- Mar 2006
ORD - 2006-03-00
LNKD- pubmed:16237462
IRN - ISSN 0969-7128 (Print)
VOL - 13
NR - 6
PG - 525 - 531
LA - eng
IW - Animals; Feasibility Studies; Gene Therapy: methods(#); Genes, Dominant(#); Genetic Diseases, Inborn: genetics(#), therapy(#); Humans; RNA Interference(#); Transduction, Genetic: methods; Trinucleotide Repeat Expansion(#)
AB - Genetic diseases that are accompanied by central nervous system involvement are often fatal. Among these are the autosomal dominant neurogenetic diseases caused by nucleotide repeat expansion. For example, Huntington's disease (HD) and spinal cerebellar ataxia are caused by expansion of a tract of CAGs encoding glutamine. In HD and the other CAG-repeat expansion diseases, the expansion is in the coding region. Myotonic dystrophy is caused by repeat expansions of CUG or CCTG in noncoding regions, and the mutant RNA is disease causing. Treatments for these disorders are limited to symptomatic intervention. RNA interference (RNAi), which is a method for inhibiting target gene expression, provides a unique tool for therapy by attacking the fundamental problem directly. In this review, we describe briefly several representative disorders and their respective molecular targets, and methods to accomplish therapeutic RNAi. Finally, we summarize studies performed to date.

7/11 - (C) MEDLINE / NLM
AN - NLM16530728
DT - Journal Article, Research Support, Non-U.S. Gov't
TI - rAAV-mediated shRNA ameliorated neuropathology in Huntington disease model mouse.
AU - Machida Yoko; Okada Takashi; Kurosawa Masaru; Oyama Fumitaka; Ozawa Keiya; Nukina Nobuyuki
PUB - Biochemical and biophysical research communications
- United States
- 28 Apr 2006
ORD - 2006-03-03
LNKD- pubmed:16530728
IRN - ISSN 0006-291X (Print)
VOL - 343
NR - 1

PG - 190 - 197
LA - eng
IW - Adenoviridae: genetics; Animals; Corpus Striatum: chemistry, metabolism, pathology; Disease Models, Animal; Dopamine and cAMP-Regulated Phosphoprotein 32: genetics, metabolism(#); Down-Regulation; Gene Therapy: methods(#); Huntington Disease: pathology, therapy(#); Mice; Nerve Tissue Proteins: antagonists & inhibitors(#), genetics; Nuclear Proteins: antagonists & inhibitors(#), genetics; RNA Interference(#); RNA, Small Interfering: genetics, pharmacology; Up-Regulation
AW - Dopamine and cAMP-Regulated Phosphoprotein 32; Hdh protein, mouse; Nerve Tissue Proteins; Nuclear Proteins; RNA, Small Interfering
AB - Huntington disease (HD) is a fatal progressive neurodegenerative disorder associated with expansion of a CAG repeat in the first exon of the gene coding the protein huntingtin (htt). Although the feasibility of RNA interference (RNAi)-mediated reduction of htt expression to attenuate HD-associated symptoms is suggested, the effects of post-symptomatic RNAi treatment in the HD model mice have not yet been certified. Here we show the effects of recombinant adeno-associated virus (rAAV)-mediated delivery of RNAi into the HD model mouse striatum after the onset of disease. Neuropathological abnormalities associated with HD, such as insoluble protein accumulation and down-regulation of DARPP-32 expression, were successfully ameliorated by the RNAi transduction. Importantly, neuronal aggregates in the striatum were reduced after RNAi transduction in the animals comparing to those at the time point of RNAi transduction. These results suggest that the direct inhibition of mutant gene expression by rAVV would be promising for post-symptomatic HD therapy.

8/11 - (C) MEDLINE / NLM
AN - NLM15235598
DT - Comparative Study, Journal Article, Research Support, Non-U.S. Gov't, Research Support, U.S. Gov't, P.H.S.
TI - RNAi suppresses polyglutamine-induced neurodegeneration in a model of spinocerebellar ataxia.
AU - Xia Haibin; Mao Qinwen; Eliason Steven L; Harper Scott Q; Martins Inês H; Orr Harry T; Paulson Henry L; Yang Linda; Kotin Robert M; Davidson Beverly L
PUB - Nature medicine
- United States
- Aug 2004
ORD - 2004-07-04
LNKD- pubmed:15235598
IRN - ISSN 1078-8956 (Print)
VOL - 10
NR - 8
PG - 816 - 820
LA - eng
IW - Adenoviridae; Animals; Blotting, Northern; Brain: metabolism; Cells, Cultured; Disease Models, Animal; Gene Expression(#); Glutamine; Immunohistochemistry; Mice; Mice, Transgenic; Nerve Degeneration: genetics(#), therapy(#); Nerve Tissue Proteins: metabolism(#), pharmacology; Nuclear Proteins: metabolism(#), pharmacology; Plasmids: genetics; Psychomotor Performance: drug effects; Purkinje Cells: drug effects, metabolism; RNA Interference: physiology(#); RNA, Messenger: metabolism(#); RNA, Small Interfering: metabolism, therapeutic use; Reverse Transcriptase Polymerase Chain Reaction; Spinocerebellar

Ataxias: pathology(#); Transduction, Genetic
AW - Nerve Tissue Proteins; Nuclear Proteins; RNA, Messenger; RNA, Small Interfering; ataxin-1; Glutamine
AB - The dominant polyglutamine expansion diseases, which include spinocerebellar ataxia type 1 (SCA1) and Huntington disease, are progressive, untreatable, neurodegenerative disorders. In inducible mouse models of SCA1 and Huntington disease, repression of mutant allele expression improves disease phenotypes. Thus, therapies designed to inhibit expression of the mutant gene would be beneficial. Here we evaluate the ability of RNA interference (RNAi) to inhibit polyglutamine-induced neurodegeneration caused by mutant ataxin-1 in a mouse model of SCA1. Upon intracerebellar injection, recombinant adeno-associated virus (AAV) vectors expressing short hairpin RNAs profoundly improved motor coordination, restored cerebellar morphology and resolved characteristic ataxin-1 inclusions in Purkinje cells of SCA1 mice. Our data demonstrate in vivo the potential use of RNAi as therapy for dominant neurodegenerative disease.

9/11 - (C) MEDLINE / NLM
AN - NLM15811941
DT - Journal Article, Research Support, Non-U.S. Gov't, Research Support, U.S. Gov't, P.H.S.
TI - RNA interference improves motor and neuropathological abnormalities in a Huntington's disease mouse model.
AU - Harper Scott Q; Staber Patrick D; He Xiaohua; Eliason Steven L; Martins Inês H; Mao Qinwen; Yang Linda; Kotin Robert M; Paulson Henry L; Davidson Beverly L
PUB - Proceedings of the National Academy of Sciences of the United States of America
- United States
- 19 Apr 2005
ORD - 2005-04-05
LNKD- pubmed:15811941
IRN - ISSN 0027-8424 (Print)
VOL - 102
NR - 16
PG - 5820 - 5825
LA - eng
IW - Animals; Cell Line; Disease Models, Animal; Gene Expression Regulation(#); Gene Silencing; Gene Therapy; Gene Transfer Techniques; Humans; Huntington Disease: genetics(#), pathology(#), therapy; Mice; Mice, Inbred Strains; Motor Activity: physiology; Nerve Tissue Proteins: genetics, metabolism(#); Nuclear Proteins: genetics, metabolism(#); RNA Interference(#)
AW - HTT protein, human; Hdh protein, mouse; Nerve Tissue Proteins; Nuclear Proteins
AB - Huntington's disease (HD) is a fatal, dominant neurogenetic disorder. HD results from polyglutamine repeat expansion (CAG codon, Q) in exon 1 of HD, conferring a toxic gain of function on the protein huntingtin (htt). Currently, no preventative treatment exists for HD. RNA interference (RNAi) has emerged as a potential therapeutic tool for treating dominant diseases by directly reducing disease gene expression. Here, we show that RNAi directed against mutant human htt reduced htt mRNA and protein expression in cell culture and in HD mouse brain. Importantly, htt gene silencing improved behavioral and neuropathological abnormalities associated with HD. Our data provide support for the further development of RNAi for HD therapy.

10/11 - (C) MEDLINE / NLM
AN - NLM16019264
DT - Journal Article, Research Support, N.I.H., Extramural, Research Support, Non-U.S. Gov't, Research Support, U.S. Gov't, P.H.S.
TI - Intrastriatal rAAV-mediated delivery of anti-huntingtin shRNAs induces partial reversal of disease progression in R6/1 Huntington's disease transgenic mice.
AU - Rodriguez-Lebron Edgardo; Denovan-Wright Eileen M; Nash Kevin; Lewin Alfred S; Mandel Ronald J
PUB - Molecular therapy : the journal of the American Society of Gene Therapy - United States - Oct 2005
ORD - 2005-10-00
LNKD- pubmed:16019264
IRN - ISSN 1525-0016 (Print)
VOL - 12
NR - 4
PG - 618 - 633
LA - eng
IW - Animals; Dependovirus: genetics(#); Disease Models, Animal; Disease Progression; Gene Expression; Gene Therapy(#); Genetic Vectors; Humans; Huntington Disease: genetics, therapy(#); Intranuclear Inclusion Bodies; Mice; Mice, Transgenic: genetics; Nerve Tissue Proteins: genetics(#), metabolism; Nuclear Proteins: genetics(#), metabolism; Phenotype; Plasmids: genetics; RNA Interference(#); RNA, Messenger: metabolism; RNA, Small Interfering: genetics, metabolism
AW - Huntington protein, mouse; Nerve Tissue Proteins; Nuclear Proteins; RNA, Messenger; RNA, Small Interfering
AB - Huntington's disease (HD) is a fatal neurodegenerative disorder caused by the presence of an abnormally expanded polyglutamine domain in the N-terminus of huntingtin. We developed a recombinant adeno-associated viral serotype 5 (rAAV5) gene transfer strategy to posttranscriptionally suppress the levels of striatal mutant huntingtin (mHtt) in the R6/1 HD transgenic mouse via RNA interference. Transient cotransfection of HEK293 cells with plasmids expressing a portion of human mHtt derived from R6/1 transgenic HD mice and a short-hairpin RNA directed against the 5' UTR of the mHtt mRNA (siHUNT-1) resulted in reduction in the levels of mHtt mRNA (-75%) and protein (-60%). Long-term in vivo rAAV5-mediated expression of siHUNT-1 in the striatum of R6/1 mice reduced the levels of mHtt mRNA (-78%) and protein (-28%) as determined by quantitative RT-PCR and Western blot analysis, respectively. The reduction in mHtt was concomitant with a reduction in the size and number of neuronal intranuclear inclusions and a small but significant normalization of the steady-state levels of preproenkephalin and dopamine- and cAMP-responsive phosphoprotein 32 kDa mRNA. Finally, bilateral expression of rAAV5-siHUNT-1 resulted in delayed onset of the rear paw clasping phenotype exhibited by the R6/1 mice. These results suggest that a reduction in the levels of striatal mHtt can ameliorate the HD phenotype of R6/1 mice.

11/11 - (C) MEDLINE / NLM
AN - NLM14980529
DT - Journal Article, Research Support, Non-U.S. Gov't, Review
TI - Molecular medicine for the brain: silencing of disease genes with RNA interference.
AU - Davidson Beverly L; Paulson Henry L
PUB - Lancet neurology

- England
- Mar 2004

ORD - 2004-03-00
LNKD- pubmed:14980529
IRN - ISSN 1474-4422 (Print)
VOL - 3
NR - 3
PG - 145 - 149
LA - eng
IW - Animals; Brain Diseases: genetics, physiopathology, therapy(#); Gene Expression Regulation: genetics; Gene Silencing: physiology(#); Gene Therapy: methods(#), trends(#); Gene Transfer Techniques: trends; Genetic Vectors: genetics, therapeutic use; Humans; RNA Interference: physiology(#); RNA, Small Interfering: genetics, therapeutic use
AW - RNA, Small Interfering
AB - The recent discovery of RNA interference (RNAi) has revolutionised biological research and now holds promise as a potential therapy for human diseases. Currently untreatable neurological diseases are especially attractive targets. Scientists have already succeeded in using RNAi to suppress dominant disease genes in vitro; in some cases, this suppression has been allele-specific, silencing the disease-causing allele while maintaining expression of the normal allele. The challenge now is to bring this powerful technology in vivo to animal models to suppress disease genes and correct disease phenotypes. In the confrontation of this challenge, research should benefit from recent advances in viral and non-viral delivery of therapy to the brain.

DEPARTAMENTO DE PATENTES E INFORMACIÓN TECNOLÓGICA. SERVICIO DE BÚSQUEDAS
Paseo de la Castellana, 75 - 28071 MADRID (ESPAÑA). Tel.: 902.157.530. FAX: 91-457-25-86. http://www.oepm.es

C) Base de Datos WPI

1/20 - (C) WPI / Thomson
AN - 2012-N94801 [74]
TI - New compound comprising an oligonucleotide, useful treating, preventing and/or delaying a human genetic disorder myotonic which is dystrophy type 1, spinocerebellar ataxia 8, and/or Huntington's disease-like 2
PN - WO2012144906 A1 20121026 DW201274
PR - US20110478096P 20110422; EP20110163581 20110422
AB - NOVELTY :
Compound comprising or consisting of the oligonucleotide sequence (NAG) m, where N is C or 5-methylcytosine and at least one occurrence of N is 5-methylcytosine and/or at least one occurrence of A comprises a 2,6-diaminopurine nucleobase modification, and where m is an integer from 4 to 15, is new.
- DETAILED DESCRIPTION :
INDEPENDENT CLAIMS are:
(1) an in vitro method for the reduction of the number of repeats CUG in transcripts of gene dystrophy type 1 (DM1)/dystrophia myotonica-protein kinase (DMPK), spinocerebellar ataxia type 8 (SCA8) or junctophilin 3 (JPH3) in a cell comprising the administration of a compound above or a pharmaceutical composition comprising the compound; and
(2) a method for alleviating one or more symptom(s) and/or characteristic(s) and/or for improving a parameter of dystrophy type 1, spinocerebellar ataxia 8 and/or Huntington's disease-like 2 caused by expansion of CUG repeats in the transcripts of DM1/DMPK, SCA8 or JPH3 genes in an individual, by administering to the individual a compound above or a pharmaceutical composition comprising the compound.
- ACTIVITY :
Muscular-Gen; Cerebroprotective; Anticonvulsant; Nootropic. Test details are described but no results given.
- MECHANISM OF ACTION :
Gene Therapy.
- USE :
The compound is useful treating, preventing and/or delaying a human genetic disorder myotonic which is dystrophy type 1, spinocerebellar ataxia 8, and/or Huntington's disease-like 2 caused by CUG repeat expansions in the transcripts of DM1/DMPK, SCA8 or JPH3 genes. The compound or pharmaceutical composition is used for the manufacture of a medicament for treating, preventing and/or delaying dystrophy type 1, spinocerebellar ataxia 8 and/or Huntington's disease-like 2 caused by expansion of CUG repeats in transcripts of the DM1/DMPK, SCA8 or JPH3 genes (all claimed).
- BIOTECHNOLOGY :
Preferred Compound: No inosine nucleotide is present. All occurrences of N are 5-methylcytosine. All occurrences of A comprise a 2,6-diaminopurine nucleobase modification. The compound comprises SEQ ID NO: 16, 17, 19, or 20. The compound comprises SEQ ID NO: 16 and has a length of 21-30 nucleotides. Sequences not defined here may be found at ftp://ftp.wipo.int/pub/published pct sequences/publication. A compound comprises a peptide part comprising Leu-Gly-Ala-Gln-Ser-Asn-Phe linked to the oligonucleotide part comprising (NAG) min which N is C or 5-methylcytosine, and where m is 4-15. The length of the oligonucleotide or oligonucleotide part

comprising (NAG) m, in which N is C or 5-methylcytosine, is from 12 till 45 nucleotides. The oligonucleotide or the oligonucleotide part comprises at least one modification, where the modification is selected from a backbone modification, a sugar modification and a base modification, when compared to an RNA-based oligonucleotide. The modification is selected from 2'-O-methyl phosphorothioate, morpholino phosphorodiamidate, locked nucleic acid and peptide nucleic acid. The oligonucleotide or oligonucleotide part is a 2'-O-methyl phosphorothioate oligonucleotide. The oligonucleotide part comprises at least one 2,6-diaminopurine, 2-thiouracil, 2-thiothymine, 5-methyluracil, 5-methylcytosine, thymine, 8-aza-7-deazaguanosine, and/or hypoxanthine. About 1-10 abasic monomers are present at a free terminus of the oligonucleotide or oligonucleotide part, the abasic monomer preferably chosen from 1-deoxyribose, 1,2-dideoxyribose, and/or 1-deoxy-2-O-methylribose, where 4 monomers of 1-deoxyribose, 1,2-dideoxyribose, and/or 1-deoxy-2-O-methylribose are present at the 3' terminus of the oligonucleotide part, preferably where the oligonucleotide or oligonucleotide part is (NAG) 7, in which N is C or 5-methylcytosine. The peptide part is linked to the oligonucleotide via a linker comprising a thioether moiety. A compound is represented by H-(X) p-(NAG) m-(Y) q-H.

N : C or 5-methylcytosine and at least one occurrence of N is 5-methylcytosine and/or at least one occurrence of A comprises a 2,6-diaminopurine nucleobase modification;
m : 4-15;
X and Y : absent, an abasic monomer or a nucleotide; and
p and q : 0-10.

- ADMINISTRATION :
Dosage is 0.01-500 mg/kg, preferably 0.5-10 mg/kg, by parenteral injections, e.g. intravenous and/or subcutaneous and/or intramuscular and/or intrathecal and/or intranasal and/or intraventricular and/or intraperitoneal, ocular, urogenital, enteral, intravitreal, intracerebral, intrathecal, epidural and/or oral administrations.

- EXAMPLE :
No suitable example given.

PAW - (PROS-N) PROSENSA TECHNOLOGIES BV
INW - AGUILERA DIEZ M B; DE VISSER P C; MULDERS S A M

2/20 - (C) WPI / Thomson
AN - 2012-K81059 [56]
TI - New nucleic acid encoding artificial primary miRNA transcript consisting of 5'-flanking region, non-guide region, loop region, guide region, and 3'-flanking region is useful for treating Huntington's disease
PN - WO2012109667 A1 20120816 DW201256
PR - US20110522632P 20110811; US20110442218P 20110212
AB - NOVELTY :
A nucleic acid encoding an artificial primary miRNA transcript (pri-miRNA) consisting of, in order of position, 5'-flanking region, non-guide region, loop region, guide region, and 3'-flanking region, is new.

- DETAILED DESCRIPTION :
A nucleic acid encoding an artificial primary miRNA transcript (pri-miRNA) consisting of, in order of position, 5'-flanking region, non-guide region, loop region, guide region, and 3'-flanking region, where the guide region is at least 90% identical to cgaccaugcgagccagca (miHDS.1 guide, SEQ ID NO: 7), agucgcugaugaccggga (miHDS.2 guide, SEQ

ID NO: 8) or acgucguaaacaagagga (miHDS.5 guide, SEQ ID NO: 9) and the non-guide region that is at least 80% complementary to the guide region, is new. INDEPENDENT CLAIMS are included for the following:
(1) new RNA encoded by nucleic acid;
(2) new expression cassette comprising a promoter contiguously linked to the nucleic acid;
(3) new vector comprising the expression cassette;
(4) new isolated nucleic acid having 80-4000 nucleotides in length comprising: either gucgaccaugcgagccagcac (SEQ ID NO: 4, miHDS.1 guide), auagucgcugaugaccgggau (SEQ ID NO: 5, miHDS.2 guide) or uuacgucguaaacaagaggaa (SEQ ID NO: 6, miHDS.5 guide); or miHDS.1 having: sequence containing 86 nucleic acids (SEQ ID NO: 1) as given in the specification, sequence containing 163 nucleic acids (SEQ ID NO: 10) as given in the specification or sequence containing 86 nucleic acids (SEQ ID NO: 33) as given in the specification, miHDS.2 having: sequence containing 85 nucleic acids (SEQ ID NO: 2) as given in the specification or sequence containing 163 nucleic acids (SEQ ID NO: 11) as given in the specification, or miHDS.5 having: sequence containing 86 nucleic acids (SEQ ID NO: 3) as given in the specification;
(5) new isolated RNA duplex comprising a guide region of nucleic acid and a non-guide region of nucleic acid, where the guide region is at least 90% identical to cgaccaugcgagccagca (miHDS.1 guide, SEQ ID NO: 7), agucgcugaugaccggga (miHDS.2 guide, SEQ ID NO: 8) or acgucguaaacaagagga (miHDS.5 guide, SEQ ID NO: 9) and the non-guide region is at least 80% complementary to the guide region;
(6) a non-human animal comprising the nucleic acid, the expression cassette, the vector, or the duplex;
(7) inducing RNA interference involving administering to a subject the nucleic acid, the expression cassette, or the vector;
(8) new isolated microRNA molecule comprising the nucleic acid having an overhang at the 3' end; and
(9) inducing low-toxicity RNA interference involving administering to a subject the nucleic acid, the expression cassette, the vector, or the duplex, where expression cassette encodes a polII promoter operably linked to a nucleic acid encoding a miRNA.

- ACTIVITY :
Anticonvulsant; Nootropic.
- MECHANISM OF ACTION :
RNA interference. No biological data given.
- USE :
In therapy, for treating Huntington's disease (claimed), neurodegenerative disease.
- ADVANTAGE :
The present invention provides improved flanking sequences that show improved efficacy over natural miR-30 flanking sequences. The use of the miRNA strategy appears to alleviate toxicity associated with traditional shRNA approaches.
- BIOTECHNOLOGY :
Preparation: No general preparation is given. Preferred Cassette: The promoter is a polII or polIII promoter. The polIII promoter is a U6 promoter, preferably mouse U6 promoter. The promoter is a tissue-specific promoter and an inducible promoter. The expression cassette further comprises a marker gene. Preferred Vector: The vector is an adeno-associated virus (AAV) vector. Preferred Duplex: The isolated RNA duplex is 19-30 base pairs in length. Preferred Molecule: In the molecule, the overhang is a 2 to 5-nucleotide repeat. The microRNA is a naturally-occurring microRNA, an artificial microRNA.

The microRNA molecule produces a decreased level of off-target toxicity. The overhang is a uu (SEQ ID NO: 26), uuu (SEQ ID NO: 27) or uuuu (SEQ ID NO: 28) sequence. The overhang is a cuu (SEQ ID NO: 29), cuuu (SEQ ID NO: 30) or cuuuu (SEQ ID NO: 31) sequence. Preferred Components: The 5'-flanking region is contiguously linked to the non-guide region, where the loop region is positioned between the non-guide region and the guide region, and the guide region is contiguously linked to the 3'-flanking region. The guide region is 15-30 nucleotides in length and the non-guide region that is at least 80% complementary to the guide region. The guide region is at least 90% identical to cgaccaugcgagccagca (miHDS.1 guide, SEQ ID NO: 7), agucgcugaugaccggga (miHDS.2 guide, SEQ ID NO: 8) or acgucguaaacaagagga (miHDS.5 guide, SEQ ID NO: 9) and the non-guide region is at least 80% complementary to the guide region. The 5'-flanking region comprises a 5'-joining sequence contiguously linked to the non-guide region, where the 5'-joining sequence consists of 5-8, preferably 7 nucleotides. The 5'-joining sequence encodes gugagcga (SEQ ID NO: 12) or gugagcgc (SEQ ID NO: 13). The 5'-flanking region further comprises a 5'-bulge sequence positioned upstream from the 5'-joining sequence, where the 5'-bulge sequence comprises a cloning site, where cloning site encodes an XhoI site. The 5'-bulge sequence consists of 1-10 nucleotides, where the 5'-bulge sequence encodes uaaacucga (SEQ ID NO: 14). The 5'-flanking region further comprises a 5'-spacer sequence positioned upstream from the 5'-bulge sequence, where the 5'-spacer sequence consists of 10-12 nucleotides. The 5'-spacer sequence is ugguaccguu (SEQ ID NO: 16). The 5'-flanking region further comprises a 5'-upstream sequence positioned upstream from the 5'-spacer sequence. The 5'-upstream sequence is 30-2000 nucleotides in length. The 3'-flanking region comprises a 3'-joining sequence contiguously linked to the guide region, where the 3'-joining sequence consists of 5-8 nucleotides. The 3'-joining sequence is at least 85% complementary to the 5'-joining sequence. The 3'-joining sequence encodes cgccuac (SEQ ID NO: 18). The 3'-flanking region further comprises a 3'-bulge sequence positioned downstream from the 3'-joining sequence. The 3'-bulge sequence comprises a cloning site, where cloning site encodes a SpeI/XbaI site or a SpeI site. The 3'-bulge sequence consists of 1-10 nucleotides, where 3'-bulge sequence encodes uag (SEQ ID NO: 32). The 5'-bulge sequence is complementary to the 3'-bulge sequence at only one nucleotide at each end of the bulge sequence. The 3'-flanking region further comprises a 3'-spacer sequence positioned downstream from the 3'- bulge sequence. The 3'-spacer sequence consists of 10-12 nucleotides. The 3'-spacer sequence is agcggccgcca (SEQ ID NO: 21). The 3'-spacer sequence is at least 70% complementary to the 5'-spacer sequence. The 3'-flanking region further comprises a 3'-downstream sequence positioned downstream from the 3'-spacer sequence. The 5'-upstream sequence does not significantly pair with the 3'-downstream sequence. The 3'-downstream sequence is 30-2000 nucleotides in length. The loop region is 15-25 nucleotides in length. The miRNA comprises a 2- or 3-nucleotide 5' or 3'-overhang. The miRNA comprises a 2-nucleotide 3'-overhang. The miRNA is an artificial miRNA.

- ADMINISTRATION :

Administration is by parenteral, intravenous, subcutaneous, intramuscular routes or by injection. No dosage details given.

- EXAMPLE :

No suitable example given.

PAW - (IOWA) UNIV IOWA RES FOUND
INW - BOUDREAU R L; DAVIDSON B L

3/20 - (C) WPI / Thomson
AN - 2012-J27468 [51]
TI - Use of DREAM protein inhibitor for treating neurodegenerative disorders including Alzheimer's disease, Huntington's disease and Down's syndrome
PN - WO2012095548 A2 20120719 DW201251
WO2012095548 A3 20121115 DW201275
PR - ES20110030033 20110113
AB - NOVELTY :
Use of a DREAM protein inhibitor is claimed for treating neurodegenerative disorders.
- ACTIVITY :
Neuroprotective; Nootropic; Anticonvulsant.
- MECHANISM OF ACTION :
None given.
- USE :
DREAM inhibitor used for treating neurodegenerative disorders including Alzheimer's disease, Huntington's disease and Down syndrome (all claimed).
- ADVANTAGE :
The DREAM inhibitor provides satisfactory treatment of neurodegenerative disorders, and prevents specific hybridization to target sequence by using DREAM protein inhibitors.
- BIOTECHNOLOGY :
Preferred Components: The inhibitor is selected from glinides, an antisense oligonucleotide, enzyme specific for deoxyribonucleic acid, specific ribozymes, specific micro ribonucleic acids, specific ribonucleic acid interference, peptide inhibitor or aptamers. The glinide is selected from a compound of formula (I) or (II) or its salt, solvate, isomer or pharmaceutically acceptable prodrug.

R 1 : pyrrolidinyl, piperidinyl, hexamethyleneimino, methyl pyrrolidinyl, dimethyl-pyrrolidinyl, 2-methyl-piperidinyl, 3-methyl-piperidinyl, 4-methyl-piperidinyl, 3,3-dimethyl-piperidinyl, cis-3,5-dimethyl-piperidinyl or trans-3,5-dimethyl-piperidinyl;
R 2 : hydrogen, halogen, methyl or methoxy group;
R 3 : hydrogen, 1-4C alkyl group, n-pentyl, 3-methyl-n-butyl or phenyl group substituted with halogen, methyl or methoxy group;
R 4 : hydrogen, methyl, ethyl or allyl group;
W 1 : methyl, hydroxymethyl, formyl, carboxy group or 2-5C alkoxycarbonyl group substituted with a phenyl group or alkoxy group;
R 1a : hydrogen, 1-5C alkyl, 6-12C aryl or aralkyl, -CH 2CO 2R 3, -CH(CH 3)-OCO-R 3, -CH 2-OCO-C(CH 3) 3or a group of formula (III);
R 2a : 1-12C aryl, 6-membered heterocyclyl, 5-membered heterocyclyl, cycloalkyl or cycloalkenyl group; and
R 3a : hydrogen or 1-5C alkyl group.
[Image]
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PAW - (CNSJ) CONSEJO SUPERIOR INVESTIGACIONES CIENTIF
- (INVE-N) CENT INVESTIGACION BIOMEDICA EN RED ENFE
- (PRIV-N) FUNDACIO PRIVADA CENT REGULACIO GENOMICA
- (CIEN-N) FUNDACION CIEN
INW - DIERSSEN SOTOS M; MELLSTROEM B; NARANJO OROVIO J R; VILLAR LOZANO D

4/20 - (C) WPI / Thomson
AN - 2012-G55808 [40]
TI - Modulating expression and aggregation of cytosine-adenosine-guanosine

expanded gene produced in a cell, involves suppressing the expression of spinocerebellar ataxia type gene or suppressor of Ty 4 homolog gene

PN - EP2463372 A1 20120613 DW201240
US2012149754 A1 20120614 DW201240

PR - TW20100143336 20101210

AB - NOVELTY :
Modulating expression of a first gene in a cell, where the first gene contains expanded cytosine-adenosine-guanosine (CAG) repeats with a repeat number more than 36, involves: suppressing the expression of a second gene, where the second gene is one selected from: spinocerebellar ataxia type (SPT) 4, SPT5, suppressor of Ty 4 homolog (SUPT4H) and suppressor of Ty 5 homolog (SUPT5H).
- DETAILED DESCRIPTION :
An INDEPENDENT CLAIM is included for identifying a compound useful for modulating a first gene, or for treating a polyglutamine disease, involving: screening several test compounds to identify one having an inhibitory activity capable of disrupting formation of an Spt4/Spt5 complex or an Supt4h/Supt5h complex, where the first gene contains expanded CAG repeats.
- ACTIVITY :
Muscular-Gen.; Anticonvulsant; Nootropic. Test details described no results given.
- MECHANISM OF ACTION :
None given.
- USE :
For modulating the expression of a first gene in a cell, for treating a polyglutamine disease, selected from Spino-cerebellar ataxia type 1, 2, 3, 7, 17, dentatorubral-pallidoluysian atrophy, spinal and bulbar muscular atrophy, and Huntington's disease (claimed).
- ADVANTAGE :
The microbial transcription elongation factor Spt4 and its mammalian ortholog, Supt4h, plays a modulating role in the expression of genes containing expanded CAG repeats. The attenuation effects of Spt4-/Supt4h deficiency is attributed to impaired transcription elongation in the CAG expanded gene, leading to decreased corresponding mRNA and protein production.
- BIOTECHNOLOGY :
Preferred Components: The first gene is selected from spinocerebellar ataxia (SCA)1, SCA2, SCA3, SCA7, SCA17, dentatorubral-pallidoluysian astrophy (DRPLA), androgen receptor (AR), and huntingtin (Htt) gene. The first gene encodes a protein containing an expanded polyglutamine stretch with more than 36 glutamine residues and form aggregates in the cell, where the cell is mammalian, preferably an animal cell or yeast cell. Preferred Method: The suppressing step is performed by a gene suppressing method selected from gene knockdown, gene knockout, and/or chemical inhibitor. The inhibiting step is performed by administering to the cell an inhibitor selected from an antibody, a small reagent, or a peptide.

DS - AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR BA ME

PAW - (UYYA-N) UNIV NAT YANG MING

INW - CHENG T; LIU C; WANG T

5/20 - (C) WPI / Thomson

AN - 2011-K32491 [55]

TI - New chemically-modified oligonucleotide, useful for treating disease associated with CAG or CUG nucleotide repeat-containing RNA, and for selectively inhibiting function of mutant nucleotide repeat containing

RNA in cell
PN - WO2011097641 A1 20110811 DW201155
PR - US20100405157P 20101020; US20100302450P 20100208; US20100302454P 20100208
AB - NOVELTY :
Chemically-modified oligonucleotide 13 to 22 nucleobases in length and having a nucleobase sequence comprising fully defined 11 bp (SEQ ID NO. 2) given in the specification and 100% complementary within a repeat region of a CAG nucleotide repeat containing RNA, is new.
- DETAILED DESCRIPTION :
Chemically-modified oligonucleotide 13 to 22 nucleobases in length and having a nucleobase sequence comprising tgctgctgctg (SEQ ID NO. 2) and 100% complementary within a repeat region of a CAG nucleotide repeat containing RNA, where: (a) each T is independently uridine or thymidine nucleoside and each comprising an independently selected high-affinity sugar modification; (b) each non-terminal G is a guanosine nucleoside comprising a 2'-deoxyribose sugar; and (c) each non-terminal C is a cytidine nucleoside comprises a 2'-deoxyribose sugar; and where one or both of the 5' or 3' terminal nucleosides of the chemically-modified oligonucleotide independently comprises one or more nuclease-resistant modifications;(d) each G is a guanosine nucleoside independently comprises a high affinity sugar modification; (e) each non-terminal T is independently a uridine or thymidine nucleoside comprising a 2'-deoxyribose sugar; (f) each terminal T is independently a uridine or thymidine nucleoside comprising a 2'deoxyribose sugar or a nuclease resistant modification; (g) each non-terminal C is a cytidine nucleoside comprising a 2'-deoxyribose sugar; and (h) each terminal C is a cytidine nucleoside comprising either a 2'deoxyribose sugar or a nuclease resistant modification, is new. INDEPENDENT CLAIMS are:
(1) a method of selectively inhibiting function of a mutant nucleotide repeat containing RNA in a cell, comprising contacting a cell having a mutant nucleotide repeat containing RNA with the chemically-modified oligonucleotide; or a method of selectively inhibiting function of a mutant nucleotide repeat containing RNA in a cell, comprising contacting a cell having or suspected having a mutant nucleotide repeat containing RNA with the chemically-modified oligonucleotide;
(2) a method of treating patient diagnosed with a disease or disorder associated with an RNA molecule containing CAG or CUG triplet repeat expansion, comprising administering to a patient diagnosed with the disease or disorder the chemically-modified oligonucleotide; and
(3) a chemically-modified oligonucleotide 13 to 22 nucleobases in length and having a nucleobase sequence comprising agcagcagcag (SEQ ID NO. 4) and 100% complementary within a repeat region of a CUG nucleotide repeat containing RNA, where each A is independently a adenosine nucleoside, each comprising an independently selected high-affinity sugar modification; each non-terminal G is a guanosine nucleoside comprising a 2'-deoxyribose sugar; each terminal G is a guanosine nucleoside comprising independently a 2'-deoxyribose sugar and/or a nuclease resistant modification; each non-terminal C is a cytidine nucleoside comprises a 2'-deoxyribose sugar; and each terminal C is a cytidine nucleoside comprising independently a 2'-deoxyribose sugar and/or a nuclease resistant modification; or each G is a guanosine nucleoside independently comprising a high affinity sugar modification; each non-terminal A is independently an adenosine nucleoside comprising a 2'-deoxyribose sugar; each terminal A is independently an adenosine nucleoside comprising a 2'deoxyribose sugar

or a nuclease resistant modification; each non-terminal C is a cytidine nucleoside comprising a 2'-deoxyribose sugar; and each terminal C is a cytidine nucleoside comprising either a 2'deoxyribose sugar or a nuclease resistant modification.

- ACTIVITY :
Anticonvulsant; Nootropic; Muscular-Gen; Cerebroprotective; CNS-Gen.
No biological data given.
- MECHANISM OF ACTION :
Gene Therapy.
- USE :
The oligonucleotide is useful for treating disease associated with CAG or CUG nucleotide repeat-containing RNA, where the disease is any of Atrophin 1, Huntington's Disease, Huntington disease-like 2 (HDL2), spinal and bulbar muscular atrophy, Kennedy disease, spinocerebellar ataxia (SCA)-1, SCA2, SCA3, SCA6, SCA7, SCA8, SCA12, SCA17, Huntington disease-like 4 (HDL4), Myotonic Dystrophy (DM1), and Machado-Joseph disease. It can also be used for selectively inhibiting function of mutant nucleotide repeat containing RNA in cell; and for treating patient diagnosed with disease or disorder associated with RNA molecule containing CAG or CUG triplet repeat expansion (all claimed).
- BIOTECHNOLOGY :
Preferred Oligonucleotide: In the chemically-modified oligonucleotide, the nuclease-resistant modification is a modified sugar moiety or a modified internucleoside linkage. The modified sugar moiety is a bicyclic sugar moiety. Each high-affinity sugar modification is a 2'-modified sugar moiety or a bicyclic sugar moiety. Each T is independently a thymidine or uridine nucleoside comprising a 4' to 2' bicyclic sugar moiety. Each 4' to 2' bridge independently comprises from 2 to 4 linked groups independently selected from -[C(R a)(R b)] y-, -C(R a)=C(R b)-, -C(R a)=N-, -C(=NR a)-, -C(=O)-, -C(=S)-, -O-, -Si(R a) 2-, -S(=O) x-, and -N(R 1)-, where x is 0, 1 , or 2; y is 1, 2, 3, or 4; each R aand R bis, independently, H, a protecting group, hydroxyl, 1-6C alkyl, substituted 1-6C alkyl, 2-6C alkenyl, substituted 2-6C alkenyl, 2-6C alkynyl, substituted 2-6C alkynyl, 5-9C aryl, substituted 5-20C aryl, heterocycle radical, substituted heterocycle radical, heteroaryl, substituted heteroaryl, 5-7C alicyclic radical, substituted 5-7C alicyclic radical, halogen, OJ 1, NJ 1J 2, SJ 1, N 3, COOJ 1, acyl (C(=O)-H), substituted acyl, CN, sulfonyl (S(=O) 2-J 1), or sulfoxyl, each J 1and J 2is, independently, H, 1-6C alkyl, substituted 1-6C alkyl, 2-6C alkenyl, substituted 2-6C alkenyl, 2-6C alkynyl, substituted 2-6C alkynyl, 5-20C aryl, substituted 5-9C aryl, acyl (C(=O)-H), substituted acyl, a heterocycle radical, a substituted heterocycle radical, 1-6C aminoalkyl, substituted 1-6C aminoalkyl or a protecting group. Each 4' to 2' bridge is independently -[C(R c)(R d)] n-, -[C(R c)(R d)] n-O-, -C(R cR d)-N(R e)-O- or -C(R cR d)-O-N(R e)-, where each R dand R dis independently hydrogen, halogen, substituted or unsubstituted 1-6C alkyl; and each R eis independently hydrogen or substituted or unsubstituted 1-6C alkyl. Each 4' to 2' bridge is independently a 4'-(CH 2) 2-2', 4'-(CH 2) 3-2', 4'-CH 2-O-2', 4'-CH(CH 3)-O-2', 4'-(CH 2) 2-O-2', 4'-CH 2-O-N(R e)-2' and 4'-CH 2-N(R e)-O-2'- bridge. Each T is a thymidine nucleoside comprising a 4'-CH(CH 3)-O-2' bicyclic sugar moiety. Each T is independently a thymidine or uridine nucleoside comprising a 2'-modified sugar moiety. The CAG nucleotide repeat containing RNA comprises 20 or more, 30 or more or 40 or more repeats. The nucleosides are linked by phosphate internucleoside linkages. At least one of the phosphate internucleoside linkages is a phosphorothioate linkage. One or both of the 5' or 3' terminal

nucleosides of the chemically-modified oligonucleotide comprises one or more nuclease-resistant modification. The nuclease-resistant modification is a modified sugar or an internucleoside linkage. The modified sugar is a bicyclic sugar moiety. Each high-affinity sugar modification is independently a 2'-modified sugar moiety or a bicyclic sugar moiety. Each G is independently a guanosine nucleoside comprising a 4' to 2' bicyclic sugar moiety. Each G is a guanosine nucleoside comprising a 4'-CH(CH 3)-O-2' bicyclic sugar moiety. Each A is independently an adenosine nucleoside comprising a 4' to 2' bicyclic sugar moiety. Each A is an adenosine nucleoside comprising a 4'-CH(CH 3)-O-2' bicyclic sugar moiety. Each A is an adenosine nucleoside comprising an independently selected 2'-modified sugar moiety. The CUG nucleotide repeat containing RNA comprises 20 or more, 30 or more or 40 or more repeats.

- ADMINISTRATION :
The chemically-modified oligonucleotide is administered by injection; injected into the central nervous system; or injected into the brain, where injection is a bollus injection, injection is an infusion, where is continuous. Preferably, administering is performed by intramuscular injection, subcutaneous injection, intravenous injection (all claimed), intrathecal, intracerebroventricular, or intraparenchymal route. No dosage details given.

- EXAMPLE :
No suitable example given.

PAW - (ISSP) ISIS PHARM INC
- (TEXA) UNIV TEXAS SYSTEM
INW - BENNETT C F; COREY D; GAGNON K; SWAYZE E E

6/20 - (C) WPI / Thomson
AN - 2011-K16354 [55]
TI - New antisense compound comprising modified antisense oligonucleotide of specifically linked nucleosides targeted to the polymorphism site, for selectively reducing allelic variant expression of gene containing single nucleotide polymorphism
PN - WO2011097643 A1 20110811 DW201155
CA2789005 A1 20110811 DW201269
AU2011213562 A1 20120823 DW201273
PR - US20100371635P 20100806; US20100302469P 20100208
AB - NOVELTY :
An antisense compound (c1) comprising modified antisense oligonucleotide (a1) including 12-30 linked nucleosides targeted to single nucleotide polymorphism (SNP) site, is new. The oligonucleotide (a1) comprises wing-gap-wing motif with 5' wing region positioned at 5' end of deoxynucleoside gap, and 3' wing region positioned at 3' end of deoxynucleoside gap, where position 5/6/7/8/9/10/11/12/13/14/15 of oligonucleotide (a1) counted from 5' terminus of the oligonucleotide (a1), or positions 1/2/3/4/5/6/7/8/9 of oligonucleotide (a1) counted from 5' terminus of the gap, aligns with SNP.

- DETAILED DESCRIPTION :
An antisense compound (c1) comprising a modified antisense oligonucleotide (a1) consisting of 12-30 linked nucleosides targeted to a single nucleotide polymorphism (SNP) site, is new. The oligonucleotide (a1) comprises a wing-gap-wing motif with a 5' wing region positioned at the 5' end of a deoxynucleoside gap, and a 3' wing region positioned at the 3' end of the deoxynucleoside gap, where position 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 of the oligonucleotide (a1) counted from 5' terminus of the oligonucleotide (a1), or positions 1, 2, 3, 4, 5, 6, 7, 8 or 9 of the oligonucleotide

(a1) counted from the 5' terminus of the gap, aligns with SNP.
INDEPENDENT CLAIMS are included for the following:
(1) selectively (m1) reducing expression of an allelic variant of a gene containing a single nucleotide polymorphism in a cell, tissue or animal, involving administering to the cell, tissue or animal a compound comprising a modified oligonucleotide complementary to a differentiating polymorphism site, where the modified oligonucleotide comprises a wing-gap-wing motif and position 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 of the modified oligonucleotide, as counted from the 5' terminus of the modified oligonucleotide, aligns with the differentiating polymorphism; and
(2) treating (m2) Huntington's disease, including selectively reducing expression of an allelic variant of a gene containing a single nucleotide polymorphism in a cell, tissue, or animal, involving administering the compound (c1) to the cell, tissue or animal, where the allelic variant is associated with Huntington's disease.

- ACTIVITY :
Anticonvulsant; Nootropic; Neuroprotective; Hypnotic; Antiparkinsonian; Muscular-Gen.; Cardiant; Respiratory-Gen.; Hepatotropic; Cytostatic; Antiinflammatory; Dermatological; Immunosuppressive; Antilipemic; Antiasthmatic; Antirheumatic; Antiarthritic; Antithyroid; Cerebroprotective; Ophthalmological; Litholytic; Antiarteriosclerotic; Cardiovascular-Gen.; Uropathic; Antianemic; Tranquilizer; Antidepressant; Hypotensive; Metabolic; CNS-Gen.; Antiarrhythmic.
- MECHANISM OF ACTION :
Antisense therapy. The efficacy of tctctattgcacattccaag (SEQ ID NO: 6) (A1) was tested by evaluating dose-dependent antisense inhibition of human huntingtin (HTT) in GM02171 cells. The compound (A1) showed IC 5 0value of 0.4 mu M.
- USE :
For selectively reducing expression of an allelic variant of a gene containing a single nucleotide polymorphism in cell, tissue or animal; and for treating Huntington's disease, Alzheimer's disease, Creutzfeldt-Jakob disease, fatal familial insomnia, Alexander disease, Parkinson's disease, amyotrophic lateral sclerosis, dentato-rubral and pallido-luysian atrophy DRPA, spino-cerebellar ataxia, Torsion dystonia, cardiomyopathy, chronic obstructive pulmonary disease (COPD), liver disease, hepatocellular carcinoma, systemic lupus erythematosus, hypercholesterolemia, breast cancer, asthma, Type 1 diabetes, rheumatoid arthritis, Graves disease, systemic lupus erythematosus, spinal and bulbar muscular atrophy, Kennedy's disease, progressive childhood posterior subcapsular cataracts, cholesterol gallstone disease, arthrosclerosis, cardiovascular disease, primary hypercalciuria, alpha-thalassemia, obsessive compulsive disorder, Anxiety, comorbid depression, congenital visual defects, hypertension, metabolic syndrome, prostate cancer, congential myasthenic syndrome, peripheral arterial disease, atrial fibrillation, sporadic pheochromocytoma, congenital malformations, Machado-Joseph disease, and autosomal dominant retinitis pigmentosa disease. The allelic variant is associated with Huntington's disease (claimed).
- ADVANTAGE :
The antisense compound selectively reduces expression of mutant allelic variants e.g. huntingtin (HTT), which are causative of disease, over the wild type variant, which appears to be necessary for normal cellular processes. The administration of an antisense compound targeted to a mutant nucleic acid results in reduction of mRNA or protein expression by at least 15, 20, 25, 30, 35, 40, 45, 50, 55, 60,

65, 70, 75, 80, 85, 90, 95 or 99%. The pharmaceutical compositions containing the compounds are co-administered with another pharmaceutical agent to produce a combinational and synergistic effect.

- BIOTECHNOLOGY :
Preparation: No general method for the preparation of the compound is given in the specification. Preferred Compounds: The compound (c1) comprises a modified oligonucleotide consisting of 18 linked nucleosides and 90% complementary to a differentiating polymorphism site, where the modified oligonucleotide comprises a wing-gap-wing motif of 4-9-5, and position 9 of the modified oligonucleotide as counted from the 5' terminus of the modified oligonucleotide, aligns with the differentiating polymorphism, and each nucleoside of each wing segment comprises a 2'-O-methoxyethyl sugar; or a modified oligonucleotide consisting of 19 linked nucleosides and 90% complementary to a differentiating polymorphism site, where the modified oligonucleotide comprises a wing-gap-wing motif of 4-11-4, where position 10 of the modified oligonucleotide as counted from the 5' terminus of the modified oligonucleotide, aligns with the differentiating polymorphism, and each nucleoside of each wing segment comprises a 2'-O-methoxyethyl sugar; or a modified oligonucleotide consisting of 15 linked nucleosides and 90% complementary to a differentiating polymorphism (where the modified oligonucleotide comprises a wing-gap-wing motif, and position 8 of the modified oligonucleotide, as counted from the 5' terminus of the modified oligonucleotide, aligns with the differentiating polymorphism), and at least one high-affinity sugar modification, where the wing-gap-wing motif is 3-9-3. Alternatively the compound (c1) is a compound (c2) comprising a modified oligonucleotide consisting of 15 to 19 (preferably 15, 17 or 19) linked nucleosides and complementary to a differentiating polymorphism site, where the modified oligonucleotide comprises a wing-gap-wing motif, and position 6, 7, 8, 9, 10, 11, 12, 13 or 14 (preferably 6, 8, 10 or 14) of the modified oligonucleotide as counted from the 5' terminus of the modified oligonucleotide, aligns with the differentiating polymorphism; and at least one high-affinity sugar modification. Preferred Components: The SNP site is on a mutant allele that is associated with a disease; and contains a differentiating polymorphism. The modified antisense oligonucleotide (a1) consists of 12-20 (preferably 15-20, especially 15-19) linked nucleosides. The position 8, 9 or 10 of the modified oligonucleotide, as counted from the 5' terminus of the modified oligonucleotide, or positions 4, 5 or 6 of the modified oligonucleotide, as counted from the 5' terminus of the gap, aligns with the single nucleotide polymorphism. The gap region is 7-11 nucleosides in length, the 5' wing region is 1-6 nucleobases in length and the 3' wing region is 1-6 nucleobases in length. The wing-gap-wing motif is any one of 5-10-5, 2-9-6, 3-9-3, 3-9-4, 3-9-5, 4-7-4, 4-9-3, 4-9-4, 4-9-5, 4-10-5, 4-11-4, 4-11-5, 5-7-5, 5-8-6, 5-9-3, 5-9-5, 5-10-4, 5-10-5, 6-7-6, 6-8-5, and 6-9-2 (preferably 2-9-6, 4-9-5, and 4-11-4). At least one internucleoside linkage is a modified internucleoside linkage. Each internucleoside linkage is a phosphorothioate internucleoside linkage. At least one nucleoside comprises a modified nucleobase which is a 5'-methylcytosine. At least one nucleoside of at least one of the wing regions comprises a modified sugar or sugar surrogate. Each of the nucleosides of each wing region comprises a modified sugar or sugar surrogate selected from a 2'-O-methoxyethyl modified sugar. At least one of the wing regions comprises a 4' to 2' bicyclic nucleoside (preferably 4'-CH(CH 3)-O-2' bicyclic nucleoside) and at least one of the remaining wing nucleosides is a non-bicyclic 2'-modified

nucleoside (preferably 2'-O-methoxyethyl nucleoside). The modified antisense oligonucleotide consists of 17 linked nucleosides, where position 9 of the modified oligonucleotide, as counted from the 5' terminus of the modified oligonucleotide, aligns with the differentiating polymorphism, and the wing-gap-wing motif is 2-9-6. The modified oligonucleotide (a1) is 100% complementary to the SNP site. In the compound (c1), at least one of the wing regions comprises a high-affinity sugar modification. The high-affinity sugar modification is a bicyclic sugar comprising a 4'-CH(CH 3)-O-2' bridge. In the compound (c2), at least one of positions 2, 3, 6, 9, 10, 11, 13 or 14 (preferably 2, 3, 13 or 14) of the modified oligonucleotide, as counted from the 5' terminus of the modified oligonucleotide, comprises the at least one high-affinity sugar modification. In the compound (c2), the wing-gap-wing motif is any of 3-9-3, 4-9-4, and 5-9-5. In the method (m1), the modified oligonucleotide is 90, 95 or 100% complementary to the single differentiating polymorphism; and the SNP site is 12-30 (preferably 15-25, 17-22, 17, 18, 19 and 20) nucleobases in length. In the method (m1), the modified oligonucleotide is a single-stranded oligonucleotide; and at least one of nucleoside positions 2, 3, 13 and 14 of the modified oligonucleotide, counting from the 5' terminus of the modified oligonucleotide, comprises a nucleoside having a bicyclic sugar comprising a 4'-CH(CH 3)-O-2' bridge. In the method (m1), the modified oligonucleotide is not a ribozyme, double stranded small interfering ribonucleic acids (siRNA), or short hairpin (shRNA); and the modified antisense oligonucleotide consists of 12-30 (preferably 15-19) linked nucleosides, where the gap region is 7 to 11 nucleosides in length, the 5' wing region is 1-6 nucleobases in length and 3' wing region is 1-6 nucleobases in length. In the method (m1) and (m2), position 8, 9 or 10 of the modified oligonucleotide, as counted from the 5' terminus of the modified oligonucleotide, or positions 4, 5 or 6 of the modified oligonucleotide, as counted from the 5' terminus of the gap, aligns with the single nucleotide polymorphism. The nucleoside immediately adjacent to and at the 5'- or 3'-side of the nucleoside that aligns with the differentiating polymorphism comprises a high-affinity sugar modification.

- ADMINISTRATION :
The compounds are administered topically (including ophthalmicly, vaginally, rectally, intranasally), orally, pulmonarily (including by inhalation or insufflations, intratracheally, intranasally, epidermally and transdermally) or parenterally (e.g. by intravenous drip, intravenous injection or subcutaneous, intraperitoneal, intraocular, intravitreal or intramuscular injection). No dosage details given.
- SPECIFIC COMPOUNDS :
151 Compounds are disclosed as the antisense compound (c1), e.g. tctctattgcacattccaag (SEQ ID NO: 6), taattttctagactttatg (SEQ ID NO: 30), atgatgagcccctctgtgt (SEQ ID NO: 50), cttttctgttgtctgtccc (SEQ ID NO: 90), and ggggacaggttgtgctctc (SEQ ID NO: 156).
- EXAMPLE :
No suitable example given.

PAW - (ISSP) ISIS PHARM INC
INW - BENNETT C F; FREIER S M; GREENLEE S; SWAYZE E E

7/20 - (C) WPI / Thomson
AN - 2011-K16394 [55]
TI - Inhibiting expression of a disease protein encoded by a messenger RNA having expanded CAG repeat region, comprises contacting a cell that

produces the disease protein with a double-stranded RNA

PN - WO2011097388 A1 20110811 DW201155

PR - US20100417048P 20101124; US20100321416P 20100406; US20100301067P 20100203

AB - NOVELTY :
Inhibiting expression of a disease protein encoded by a messenger RNA (mRNA) having expanded CAG repeat region, comprises contacting a cell that produces the disease protein with a double-stranded RNA of 15-30 bases that targets the expanded CAG repeat region of a disease protein mRNA, and the double-stranded RNA further contains 1, 2, 3, 4 or 5 base mismatches as compared to the CAG repeat.

- DETAILED DESCRIPTION :
Inhibiting expression of a disease protein encoded by a messenger RNA (mRNA) having expanded CAG repeat region, comprises contacting a cell that produces the disease protein with a double-stranded RNA of 15-30 bases that targets the expanded CAG repeat region of a disease protein mRNA, and the double-stranded RNA further contains 1, 2, 3, 4 or 5 base mismatches as compared to the CAG repeat, where (i) inhibiting is selective for the disease protein expression over expression of a normal form of the disease protein, an mRNA for the normal form which lacks the expanded CAG repeat region, (ii) and the double-stranded RNA contains no more than one base mismatch in a seed sequence. An INDEPENDENT CLAIM is a composition of matter comprising a double-stranded RNA of 15-30 bases that targets the expanded CAG repeat region of a disease protein mRNA, and the double-stranded RNA further contains 1, 2, 3, 4 or 5 base mismatches as compared to the CAG repeat, where the double-stranded RNA contains no more than one base mismatch in a seed sequence.

- ACTIVITY :
Anticonvulsant; Nootropic. No biological data given.

- MECHANISM OF ACTION :
Huntingtin Inhibitor; Ataxin-3 Inhibitor; Ataxin-1 Inhibitor; Ataxin-2 Inhibitor; Atrophin1 Inhibitor; Protease Inhibitor; Gene Therapy.

- USE :
The method and composition are useful for inhibiting expression of a disease protein encoded by an mRNA having expanded CAG repeat region (claimed); and for treating Huntington's disease.

- ADVANTAGE :
The method selectively inhibits protein expression of CAG repeat-related disease proteins such as Huntingtin Disease protein and Ataxin-3 using double-stranded RNAs and nucleic acid analogs.

- BIOTECHNOLOGY :
Preferred Method: In inhibiting expression of the disease protein encoded by the mRNA having expanded CAG repeat region, the CAG repeat region is 125 repeats or less in size. The double-stranded RNA is 19-21 bases in length. The disease protein is Huntingtin, ataxin-3, ataxin-1, ataxin-2 or atrophin1. The double-stranded RNA comprises one or more chemically-modified bases, where the chemically-modified base is a 2'-O-methyl modified nucleotide, a nucleotide comprising a 5'-phosphorothioate group, and a terminal nucleotide linked to a cholesteryl derivative or dodecanoic acid bisdecylamide group, a 2'-deoxy-2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an abasic nucleotide, 2'-amino-modified nucleotide, 2'-alkyl-modified nucleotide, morpholino nucleotide, a phosphoramidate, or a non-natural base comprising nucleotide. The guide strand or the passenger strand contains the chemically-modified base. The guide and passenger strands both contain at least one chemically-modified base. The double-stranded RNA further

targets a repeat region junction, where the double-stranded RNA comprises at least 15 bases and the first base mismatch is flanked by at least 7 bases on both the 5' and 3' ends of the double-stranded RNA. The first base mismatch is in the guide strand. The double-stranded RNA further comprises a second base mismatch, where the second base mismatch is in the passenger strand. The first and second base mismatches are in the guide strand. The double-stranded RNA comprises at least 16 bases and the first and second base mismatches are adjacent and flanked by at least 7 bases on both the 5' and 3' ends of the double-stranded RNA. The double-stranded RNA is at least 19 bases in length and the second base mismatch is located within base 9 to the 3' terminus. Also, both the first and second base mismatches are located within base 9 to the 3' terminus. The double-stranded RNA is at least 19 bases in length further comprises second and third base mismatches in the guide strand within base 9 to the 3' terminus. All of the, first, second and third base mismatches are located within base 9 to the 3' terminus. The double-stranded RNA is at least 19 bases in length and further comprises second, third and fourth base mismatches in the guide strand within base 9 to the 3 ' terminus. All of the first, second, third and fourth base mismatches are located within base 9 to the 3' terminus. The double-stranded RNA is at least 19 bases in length and further comprises second, third, fourth and fifth base mismatches in the guide strand within base 9 to the 3' terminus. All of the first, second, third, fourth and fifth base mismatches are located within base 9 to the 3' terminus. Inhibiting does not substantially affect production of the disease protein mRNA. The selectivity is 5-fold to 40-fold, preferably 20-fold to 40-fold. The double-stranded RNA comprises a non-natural internucleotide linkage, where the non-natural internucleotide linkage is a phosphorothioate linkage. The double-stranded RNA further comprises an inserted base as compared to the CAG repeat. Alternatively, inhibiting expression, in a subject, of the disease protein encoded by the mRNA having expanded CAG repeat region comprises administering to the subject an amount of a double-stranded RNA of 15-30 bases that targets the expanded CAG repeat region of a disease protein mRNA, and the double-stranded RNA further contains 1, 2, 3, 4 or 5 base mismatches as compared to the CAG repeat, where (i) inhibiting is selective for the disease protein expression over expression of a normal form of the disease protein, an mRNA for the normal form which lacks the expanded CAG repeat region, (ii) and the double-stranded RNA contains no more than one base mismatch in a seed sequence. The double-stranded RNA is administered more than once, where the double-stranded RNA is administered in a saline formulation or a lipid formulation. The method further comprises administering a second therapy to the subject. Preferred Composition: In the composition, the double-stranded RNA is dispersed in a saline vehicle or a lipid vehicle. The double-stranded RNA further comprises an inserted base as compared to the CAG repeat. The double-stranded RNA is selected from: fully defined 21 bp (SEQ ID NOS: 1-109), given in the specification. gcugcugaugcugcugcugtt (SEQ ID NO: 1) ttcgacgacuacgacgacgac (SEQ ID NO: 2) gcugcugcagcugcugcugtt (SEQ ID NO: 3) ttcgacgacgucgacgacgac (SEQ ID NO: 4) gcugcugcuacugcugcugtt (SEQ ID NO: 5) ttcgacgacgaugacgacgac (SEQ ID NO: 6) gcugcugcuucugcugcugtt (SEQ ID NO: 7) ttcgacgacgaagacgacgac (SEQ ID NO: 8) gcugcugcugaugcugcugtt (SEQ ID NO: 9) ttcgacgacgacuacgacgac (SEQ ID NO: 10).

- ADMINISTRATION :

Administration of the composition can be through oral, parenteral, intracranial, intraparenchymal, intraventricular, intrathecal,

epidural, intravenous, intraarterial, intramuscular, intraperitoneal, subcutaneous, transdermal, airway, nasal, rectal, vaginal, topical, buccal or sublingual routes. No dosage details given.
- EXAMPLE :
No suitable example given.

PAW - (TEXA) UNIV TEXAS SYSTEM
- (ALNY-N) ALNYLAM PHARM INC
INW - COREY D R; HU J; SAH D W Y

8/20 - (C) WPI / Thomson
AN - 2011-J24438 [48]
TI - Treating a subject having or at risk for a disease caused by a gain-of-function mutant protein, comprises administering to the subject an effective amount of a RNA interference agent targeting an allelic polymorphism
PN - US2011172291 A1 20110714 DW201148
PR - US20100966525 20101213; US20090348794 20090105; US20080571705 20081209; WO2007US15638 20070709; US20060819704P 20060707; WO2004US29968 20040913; US20030502678P 20030912
AB - NOVELTY :
Treating a subject having or at risk for a disease characterized or caused by a gain-of-function mutant protein, comprises: administering to the subject an effective amount of a RNA interference (RNAi) agent targeting an allelic polymorphism within a gene encoding the mutant protein, such that sequence-specific interference of the gene occurs; thus treating the disease in the subject.
- DETAILED DESCRIPTION :
INDEPENDENT CLAIMS are:
(1) an RNAi agent comprising a first strand comprising 16-25 nucleotides homologous to a region of a gene encoding a gain-of-function mutant protein, the region comprising an allelic polymorphism, and a second strand comprising 16-25 nucleotides complementary to the first strand, where the RNAi agent direct target-specific cleavage of a mRNA transcribed from the gene encoding the mutant protein;
(2) an isolated nucleic acid molecule encoding the RNAi agent;
(3) a vector comprising the nucleic acid molecule;
(4) a host cell comprising the RNAi agent, and/or the vector;
(5) a composition comprising the RNAi agent, and a pharmaceutically acceptable carrier;
(6) a method of silencing a target mRNA encoding a mutant huntingtin (htt) protein in a cell, comprising contacting the cell with effective amount of a RNA silencing agent targeting a heterozygous single nucleotide polymorphism (SNP) within the target mRNA, such that RNA silencing of the messenger RNA (mRNA) occurs, where the SNP has an allelic frequency of at least 35% in a sample population;
(7) an RNA silencing agent comprising an antisense strand comprising 16-25 nucleotides homologous to a region of an mRNA encoding a mutant htt protein, the region comprising a heterozygous SNP having an allelic frequency of at least 35% in a sample population, where the RNA silencing agent is capable of directing RNA silencing of the mRNA; and
(8) a small interfering RNA (siRNA) selected from: (a) an siRNA comprising (i) a sense strand comprising the sequence of ucccucauccacugugugaac (SEQ ID NO: 34) or a variant; and (ii) an antisense strand comprising the sequence of gcacacaguggaugagggagc (SEQ ID NO: 35) or a variant, the variant comprising at least one nucleotide analog or backbone modification; (b) an siRNA comprising

(i) a sense strand comprising the sequence of ucccucaucuacugugugaac (SEQ ID NO: 38) or a variant; and (ii) an antisense strand comprising the sequence of cgagggaguagaugacacacg (SEQ ID NO: 39) or a variant, the variant comprising at least one nucleotide analog or backbone modification; (c) an siRNA comprising (i) a sense strand comprising the sequence of gggacaguaauucaacgcguc (SEQ ID NO: 40) or a variant; and (ii) an antisense strand comprising the sequence of agcguugaauuacugucccca (SEQ ID NO: 41) or a variant, the variant comprising at least one nucleotide analog or backbone modification; and (d) an siRNA comprising (i) a sense strand comprising the sequence of gggacaguacuucaacgcguc (SEQ ID NO: 44) or a variant; and (ii) an antisense strand comprising the sequence of accccugucaugaaguugcga (SEQ ID NO: 45) or a variant, the variant comprising at least one nucleotide analog or backbone modification.

- ACTIVITY :
Anticonvulsant; Nootropic; Cerebroprotective; Muscular-Gen; Immunostimulant. No biological data given.
- MECHANISM OF ACTION :
RNA Interference; Protease Inhibitor; Vaccine.
- USE :
The methods, RNAi agent, and composition are useful for treating a subject having or at risk for a disease characterized or caused by a gain-of-function mutant protein, where the disease is selected from Huntington's disease, spino-cerebellar ataxia type 1, 2, 3, 6, 7, 8, and/or 12, fragile X syndrome, fragile XE MR, Friedreich ataxia, myotonic dystrophy, spinal bulbar muscular disease and dentatoiubral-pallidoluysian atrophy; and for silencing a target mRNA encoding a mutant htt protein in a cell (all claimed).
- ADVANTAGE :
The method and agents provide effective treatment for a variety of gain-of-function diseases.
- BIOTECHNOLOGY :
Preferred Method: In treating the subject having or at risk for the disease characterized or caused by the gain-of-function mutant protein, the gene comprises an expanded trinucleotide repeat region, and the mutant protein comprises an expanded polyglutamine domain. The RNAi agent targets an allelic polymorphism within the gene encoding a huntingtin protein. The RNAi agent targets a polymorphism selected from P1-P5, and P6-P43. The RNAi agent comprises a first strand comprising 16-25 nucleotides homologous to a region of the gene comprising the polymorphism and a second strand comprising 16-25 nucleotides complementary to the first strand. The effective amount is an amount effective to inhibit the expression or activity of the mutant protein. Alternatively, treating the disease or disorder in the subject caused by the gain-of function mutant protein comprises identifying an allelic polymorphism within a gene encoding the mutant protein and administering to the subject an RNAi agent targeting the polymorphism such that the mutant protein is decreased, thus treating the subject. In silencing the target mRNA encoding the mutant htt protein in the cell, the SNP is present at genomic site RS362331. The target mRNA comprises the sequence of fully defined 40 bp (SEQ ID NO: 36 or 37), given in the specification. The RNA silencing agent is capable of inducing discriminatory RNA silencing. The antisense strand of the RNA silencing agent is complementary to the SNP and where the RNA silencing agent is capable of substantially silencing the mutant htt protein without substantially silencing the corresponding wild-type htt protein. The sample population is of Western European origin. Alternatively, silencing the target mRNA encoding the mutant

htt protein in the cell, comprises contacting the cell with an effective amount of a small interfering RNA (siRNA) targeting a heterozygous SNP within the target mRNA, such that RNA silencing of the mRNA occurs, where the siRNA is selected from: (a) an siRNA comprising (i) a sense strand comprising the sequence of ucccucauccacugugugaac (SEQ ID NO: 34) or a variant; and (ii) an antisense strand comprising the sequence of gcacacaguggaugagggagc (SEQ ID NO: 35) or a variant, the variant comprising at least one nucleotide analog or backbone modification; (b) an siRNA comprising (i) a sense strand comprising the sequence of ucccucaucuacugugugaac (SEQ ID NO: 38) or a variant; and (ii) an antisense strand comprising the sequence of cgagggaguagaugacacacg (SEQ ID NO: 39) or a variant, the variant comprising at least one nucleotide analog or backbone modification; (c) an siRNA comprising (i) a sense strand comprising the sequence of gggacaguaauucaacgcguc (SEQ ID NO: 40) or a variant; and (ii) an antisense strand comprising the sequence of agcguugaauuacugucccca (SEQ ID NO: 41) or a variant, the variant comprising at least one nucleotide analog or backbone modification; and (d) an siRNA comprising (i) a sense strand comprising the sequence of gggacaguacuucaacgcguc (SEQ ID NO: 44) or a variant; and (ii) an antisense strand comprising the sequence of accccugucaugaaguugcga (SEQ ID NO: 45) or a variant, the variant comprising at least one nucleotide analog or backbone modification. The siRNA comprises a lipophilic moiety, where the lipophilic moiety is a cholesterol moiety. Preferred Agent: The RNAi agent targets a polymorphism within the gene encoding a Huntington protein. The first strand comprises a nucleotide sequence identical to the sequence of the polymorphism. The RNAi agent further comprises a loop portion comprising 4-11 nucleotides that connects the two strands. The RNA silencing agent is a siRNA, where the siRNA comprises a sense strand having a nucleotide sequence identical to the sequence of the SNP. The sense strand of the siRNA is identical to the polymorphism at a nucleotide position that is 10-16 nucleotides from the 5' end of the antisense strand. Preferred Vector: The vector is a viral vector, retroviral vector, expression cassette, or plasmid. The vector further comprises an RNA Polymerase III or RNA Polymerase II promoter, where the RNA Polymerase III promoter is the U6 or Hi promoter. Preferred Host Cell: The host cell is a mammalian host cell, a non-human mammalian cell, or a human cell.

- ADMINISTRATION :
Dosage is 0.1-2 mg/kg. Administration can be through inhalation, topical, intravenous, intramuscular, intrathecal, nasal, buccal, pulmonary, oral, intradermal, subcutaneous, intraperitoneal, transdermal, or transmucosal route.

PAW - (UMAC) UNIV MASSACHUSETTS
INW - ARONIN N; ZAMORE P D

9/20 - (C) WPI / Thomson
AN - 2011-C66654 [25]
TI - New compound for treating Huntington's disease, neurological disorders, muscle atrophy, cardiac failure, weight loss, osteoporosis, and testicular atrophy, comprising modified oligonucleotide
PN - WO2011032045 A1 20110317 DW201125
AU2010292003 A1 20120419 DW201231
CA2773886 A1 20110317 DW201231
EP2475675 A1 20120718 DW201247
MXPA12003006 A 20120630 DW201253
US2012252879 A1 20121004 DW201266

CN102625809 A 20120801 DW201271
KR20120120511 A 20121101 DW201274
PR - US20090241853P 20090911; US201213395188 20120530
AB - NOVELTY :
A compound comprising a modified oligonucleotide containing 12-30 linked nucleosides, where the linked nucleosides comprise at least 8 contiguous nucleobases of SEQ ID NOs: 6, 9, 10, 11, 12, 13, 14, 15, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 32, 33, 35 and 36, is new.
- DETAILED DESCRIPTION :
A compound comprising a modified oligonucleotide containing 12-30 linked nucleosides, where the linked nucleosides comprise at least 8 contiguous nucleobases of SEQ ID NOs: 6, 9, 10, 11, 12, 13, 14, 15, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 32, 33, 35, and 36, is new. tagcattcttatctgcacgg (SEQ ID NO: 6), acccgtaactgaaccagctg (SEQ ID NO: 7), ttccctgaactggcccactt (SEQ ID NO: 8), ctctgattccctgaactggc (SEQ ID NO: 9), gcctctgattccctgaactg (SEQ ID NO: 10), tgcctctgattccctgaact (SEQ ID NO: 11), tgcctctgattccctgaact (SEQ ID NO: 11), ttgcctctgattccctgaac (SEQ ID NO: 12), attgcctctgattccctgaa (SEQ ID NO: 13), tggaatgattgcctctgatt (SEQ ID NO: 14), gtttggaatgattgcctc (SEQ ID NO: 15), ccaatgatctgttttgaatg (SEQ ID NO: 16), gccttccttccactggccat (SEQ ID NO: 17), ctgcatcagctttatttgtt (SEQ ID NO: 18), cctgcatcagctttatttgt (SEQ ID NO: 19), agctcttttcctgcatcagc (SEQ ID NO: 20), gtaacattgacaccacca (SEQ ID NO: 21), ctcagtaacattgacaccac (SEQ ID NO: 22), atgagtctcagtaacattga (SEQ ID NO: 23), tccttgtggcactgctgcag (SEQ ID NO: 24), ttctccttgtggcactgctg (SEQ ID NO: 25), tcattctccttgtggcactg (SEQ ID NO: 26), attctccttgtggcactg (SEQ ID NO: 27), cgagacagtcgcttccactt (SEQ ID NO: 28), tgtcgagacagtcgcttc (SEQ ID NO: 29), ttgcacattccaagtttggc (SEQ ID NO: 30), tctctattgcacattccaag (SEQ ID NO: 31), tttctctattgcacattcca (SEQ ID NO: 32), tctctattgcacattcca (SEQ ID NO: 33), gcagggttaccgccatcccc (SEQ ID NO: 34), accttatctgcacggttc (SEQ ID NO: 35) and ctctctgtgtatcaccttcc (SEQ ID NO: 36). INDEPENDENT CLAIMS are included for the following:
(1) composition comprising the above-cited compound or its salt and at least one of a carrier or diluent;
(2) method (M1) for administering the above-cited compound or composition to animal;
(3) method (M2) to reduce Huntingtin mRNA or protein expression in animal, involves administering the above-cited compound or composition to animal;
(4) method (M3) for treating human with Huntington's disease, involves identifying the human with the disease and administering the above-cited compound or composition;
(5) method (M4) for ameliorating symptom of Huntington's disease, involves administering the above-cited compound to a human in need, where the modified oligonucleotide specifically hybridizes with SEQ ID NO: 1;
(6) method (M5) for reducing the rate of progression of symptom associated with Huntington's Disease, involves performing the above-cited method (M4); and
(7) method (M6) for reversing degeneration indicated by a symptom associated with Huntington's disease, involves performing the above-cited method (M4).
- ACTIVITY :
Anticonvulsant; Nootropic; Neuroprotective; Hypnotic; Neuroleptic; Tranquilizer; Antidepressant; Muscular-Gen; Cardiant; Anorectic; Osteopathic.

- MECHANISM OF ACTION :
RNA interference. In a test for measuring suppression of mRNA using GM04281 fibroblast cells, using antisense oligonucleotide of SEQ ID NO: 31 exhibited IC 5 0value of 0.22 mu M.
- USE :
The compound is useful for treating Huntington's disease and symptoms, neurological disorder, restlessness, lack of coordination, unintentionally initiated motions, unintentionally uncompleted motions, unsteady gait, chorea, writhing motions, abnormal posturing, instability, abnormal facial expressions, difficulty in chewing, swallowing, and speaking, seizure, sleep disorder, impaired planning, flexibility, abstract thinking, glucose tolerance, rule acquisition, initiation of appropriate actions, inhibition of inappropriate actions, short-term memory, and long-term memory, paranoia, disorientation, confusion, hallucination, dementia, anxiety, depression, blunted affect, egocentrisms, aggression, compulsive behavior, irritability, suicidal ideation, reduced brain mass, muscle atrophy, cardiac failure, weight loss, osteoporosis, and testicular atrophy in human. The method (M2) is useful for reducing Huntingtin mRNA or protein expression in animal. The method (M6) is useful for reversing degeneration indicated by a symptom associated with Huntington's disease. The symptom is chosen from physical symptom, cognitive symptom, psychiatric symptom, and peripheral symptom (all claimed).
- BIOTECHNOLOGY :
Preparation: No preparation method is given. Preferred Nucleotide: The modified oligonucleotide comprises 15-25 linked nucleosides, preferably 18-21 linked nucleosides. The modified oligonucleotide comprises 12-30 linked nucleosides, where the linked nucleosides comprise at least 8 contiguous nucleobase portion complementary with position chosen from 4384-4403, 4605-4624, 4607-4626, 4608- 4627, 4609-4628, 4610-4629, 4617-4636, 4622-4639, 4813-4832, 4814-4833, 4823-4842, 4860-4877, 4868-4887, 4925-4944, 4928-4947, 4931-4950, 4931-4948, 4955-4974, 4960-4977, 5801-5820, 5809-5828, 5809-5826, 101088-101105, 115066-115085, 4607-4626, 4608-4627, 4609- 4628, 4610-4629, 4813-4832, 4862-4881, 5809-5828 and 4928-4947 of SEQ ID NO: 1. The nucleobase sequence comprises at least 15, preferably 18 contiguous nucleobases of SEQ ID NOs: 6, 9, 10, 11, 12, 13, 14, 15, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 32, 33, 35, or 36, preferably 12, 22, 28, 30, 32, and 33. The modified oligonucleotide is a single-stranded oligonucleotide. The nucleobase sequence of the modified oligonucleotide is chosen from at least one of 90%, 95% and 100% complementary to SEQ ID NO: 1. The compound comprises at least one intemucleoside linkage. The intemucleoside linkage is a modified intemucleoside linkage, preferably phosphorothioate intemucleoside linkage. The compound comprises at least one nucleoside of the modified oligonucleotide containing a modified sugar and at least one tetrahydropyran modified nucleoside, where tetrahydropyran ring replaces furanose ring. The tetrahydropyran modified nucleoside of formula (III), where B xis optionally protected heterocyclic base moiety. The nucleoside comprises a modified nucleobase, preferably 5-methyl cytosine. The modified oligonucleotide comprises a gap segment consisting of 10 linked deoxynucleosides, preferably 8 linked deoxynucleosides, a 5' wing segment consisting of 5 linked nucleosides, preferably 6 linked deoxynucleosides and a 3' wing segment consisting of 5 linked nucleosides, preferably 6 linked deoxynucleosides, where the gap segment is positioned between the 5' wing segment and the 3' wing segment, wherein each nucleoside of each

wing segment comprises a 2'-O-methoxyethyl sugar. The modified oligonucleotide comprises 20 linked nucleosides. Preferred Sugar: The modified sugar is bicyclic sugar. The bicyclic sugar comprises compound of formula: 4'-CH 2-N(R)-O-2' (I) bridge, where R is H, 1-12C alkyl, or protecting group. The bicyclic sugar comprises compound of formula: 4'-CH(CH 3)-O-2' (II) bridge. Preferred Method: The method (M1) further involves co-administering the above-cited compound or composition and second agent. The compound is administered to CNS.
[Image]
- EXAMPLE :
No suitable example given.

DS - AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO SE SI SK SM TR

PAW - (GENZ) GENZYME CORP
- (ISSP) ISIS PHARM INC
- (BENN-I) BENNETT C F
- (CHEN-I) CHENG S H
- (CLEV-I) CLEVELAND D W
- (FREI-I) FREIER S M
- (HUNG-I) HUNG G
- (KORD-I) KORDASIEWICZ H
- (SHIH-I) SHIHABUDDIN L
- (STAN-I) STANEK L

INW - BENNETT C; BENNETT C F; CHENG S; CHENG S H; CLEVELAND D; CLEVELAND D W; FREIER S; FREIER S M; HUNG G; KORDASIEWICZ H; SHIHABUDDIN L; STANEK L

10/20 - (C) WPI / Thomson

AN - 2010-N07842 [69]

TI - Silencing mutant huntingtin (htt) mRNA in a Huntington's disease (HD) patient population comprises administering to a population RNA silencing agent targeting an HD-associated htt single nucleotide polymorphism

PN - WO2010118263 A1 20101014 DW201069
US2012136039 A1 20120531 DW201236

PR - US20090167861P 20090408; US201213263961 20120130

AB - NOVELTY :
Silencing mutant huntingtin (htt) mRNA in a Huntington's disease (HD) patient population comprises administering to the patient population an amount of a first RNA silencing agent targeting an HD-associated htt single nucleotide polymorphism (SNP) in combination with one or more RNA silencing agents targeting other htt SNPs, such that RNA silencing of the mRNA occurs, the one or more other htt SNPs having frequency of heterozygosity of at least 20%, 30%, 35% or more in a sample population.
- DETAILED DESCRIPTION :
INDEPENDENT CLAIMS are:
(1) a kit comprising (a) a first RNA silencing agent targeting an HD-associated htt SNP, (b) one or more additional RNA silencing agents targeting other htt SNPs having a frequency of heterozygosity of at least 20%, 30%, 35% or more in a sample population, and (c) instructions for administration of one or more of the RNA silencing agents to a subject having HD;
(2) a kit comprising (a) one or more siRNAs comprising a guide strand and a complementary strand, where the guide strand has a nucleotide sequence set forth in Table 6 (SEQ ID NOs: 208-233), and (b) instructions for its use for silencing mutant htt mRNA in a subject having HD; and

(3) a small interfering RNA (siRNA) comprising a guide strand and a complementary strand, where the guide strand has a nucleotide sequence set forth in Table 6 (SEQ ID NOs: 208-233).

- ACTIVITY :
Anticonvulsant; Nootropic. Tests are described, but no results are given.
- MECHANISM OF ACTION :
RNA Interference; Gene Therapy.
- USE :
The method and kit are useful for silencing mutant htt mRNA in an HD patient population (claimed) and for treating HD.
- ADVANTAGE :
The present invention provides RNA silencing technology (e.g. RNA interference) against such SNPs optimally combined with select additional SNP targeting silencing agents, thus resulting in an effective treatment of significantly-sized patient populations. It also provides silencing agents having enhanced discriminatory properties.
- BIOTECHNOLOGY :
Preferred Method: In the method of silencing mutant htt mRNA in an HD patient population, the HD-associated htt SNP is present at genomic site rs362307. The other htt SNPs are as set forth in any of Tables 1, 2, 5 and 6. The other htt SNPs are selected from rs4690074, rs362336, rs362331, rs362373, rs362272, rs362306, rs362268, and rs362267. The patient population is of US or Western European origin. Silencing mutant htt mRNA in 70% or more HD patients in an HD patient population comprises administering to the patients in the HD patient population one or more RNA silencing agents, where each RNA silencing agent targets an htt SNP having a frequency of heterozygosity of at least 20% or more in a sample HD patient population, such that RNA silencing of the mRNA occurs in 70% or more patients in the HD patient population. The method further comprises identifying the sequence of the nucleotide located at one or more SNPs selected from rs362307, rs363125 and rs362273 in the mutant htt mRNA of the HD patients in the HD patient population. The RNA silencing agents target SNP1, SNP2, and SNP3 as set forth in Table 2. Silencing mutant htt mRNA in 70% or more HD patients in an HD patient population comprises administering to the patients in the HD patient population one or more RNA silencing agents, where each RNA silencing agent targets an htt SNP selected from rs362307, rs363125 and rs362273, such that RNA silencing of the mRNA occurs in 70% or more patients in the HD patient population. The RNA silencing agent is an siRNA or a short hairpin RNA (shRNA). The method further comprises identifying the sequence of the nucleotide located at one or more SNPs selected from rs362307, rs363125 and rs362273 in the mutant htt mRNA of the HD patients in the HD patient population. A nucleotide complementary to the SNP in the mutant htt mRNA is located at position 10 relative to the 5' end of the antisense strand of the RNA silencing agent. The RNA silencing agent further comprises a mismatch with respect to both the mutant htt mRNA and the wild-type htt mRNA at one or more positions located within the seed sequence of the RNA silencing agent. One or more positions are selected from position 2, position 3, position 4, position 5, position 6, and position 7 relative to the 5' end of the antisense strand of the RNA silencing agent. Silencing mutant htt mRNA in 70% or more HD patients in a RD patient population comprises administering to the patients in the HD patient population one or more siRNAs each comprising a guide strand and a complementary strand, where the guide strand is selected from SEQ ID NO: 210, 211, 220, 230, and 233, such

that RNA silencing of the mRNA occurs in 70% or more patients in the HD patient population. Sequences not defined here may be found at ftp://ftp.wipo.int/pub/published pct sequences/publication. Preferred Kit: The first silencing agent targets htt SNP rs362307, and the additional RNA silencing agents target htt SNPs rs363125 and rs362273.

- ADMINISTRATION :
Dosage is 0.00001-10 mg/kg by parenteral, e.g., intravenous, intradermal, subcutaneous, oral (e.g., inhalation), transdermal (topical), transmucosal, and rectal administration.

PAW - (UMAC) UNIV MASSACHUSETTS
INW - ARONIN N; PFISTER E; ZAMORE P D

11/20 - (C) WPI / Thomson
AN - 2009-R25444 [78]
TI - Reducing expression of a mutant huntingtin (mHTT) protein in a cell by contacting the cell with an amount of a nucleic acid silencing agent targeting a differentiating polymorphism in RNA encoding the mHTT
PN - WO2009135322 A1 20091112 DW200978
AU2009244013 A1 20091112 DW201107
CA2726866 A1 20091112 DW201120
EP2297341 A1 20110323 DW201121
US2011213010 A1 20110901 DW201159
HK1154911 A0 20120504 DW201252
PR - US20080714652P 20080509; US20080071652P 20080509; US20110991883 20110506
AB - NOVELTY :
Reducing expression of a mutant huntingtin (mHTT) protein in a cell comprises contacting the cell with an amount of a nucleic acid silencing agent targeting a differentiating polymorphism in RNA encoding the mHTT.

- DETAILED DESCRIPTION :
INDEPENDENT CLAIMS are:
(1) a method of selecting a nucleic acid silencing agent targeting a differentiating polymorphism in RNA encoding a mHTT protein of a subject comprising: (a) obtaining a nucleic acid sample from the subject; (b) identifying one or more differentiating polymorphisms in the nucleic acid sample; (c) selecting a nucleic acid silencing agent comprising a sequence that preferentially targets the one or more differentiating polymorphism in the RNA encoding a mHTT protein;
(2) a method of reducing expression of a mHTT protein in a subject comprising: (a) obtaining a nucleic acid sample from the subject; (b) identifying one or more than one differentiating polymorphisms in the nucleic acid sample; (c) selecting one or more than one nucleic acid silencing agents comprising a sequence that preferentially targets the one or more than one differentiating polymorphism in the RNA encoding a mHTT protein; and (d) administering to the subject an effective amount of the one or more than one nucleic acid silencing agent; and
(3) a method of screening for a nucleic acid silencing agent targeting a differentiating polymorphism in RNA encoding a mHTT protein in a subject comprising: (a) providing a cell heterozygous for a differentiating polymorphism in a nucleic acid sequence encoding HTT; (b) contacting the cell with one or more candidate nucleic acid silencing agents targeting the differentiating polymorphism; (c) assaying the cell for HTT and mHTT RNA, protein or RNA and protein expression; and (d) determining the one or more nucleic acid silencing agents from the candidate nucleic acid silencing agents.

- ACTIVITY :

Anticonvulsant; Nootropic. Test details are described but no results given.
- MECHANISM OF ACTION :
Huntingtin-Inhibitor; RNA-Interference.
- USE :
The methods are useful for reducing expression of a mHTT protein in a cell or in a subject and selecting a nucleic acid silencing agent targeting a differentiating polymorphism in RNA encoding a mHTT protein of a subject (all claimed). The methods are useful for the treatment of Huntington's disease.
- BIOTECHNOLOGY :
Preferred Method: In the methods above, the differentiating polymorphism is a single nucleotide polymorphism (SNP). The nucleic acid silencing agent is an oligonucleotide selected from any one of fully defined sequences comprising approximately 50 bp (SEQ ID NO. 68-134) given in the specification, or its fragment. The sequence of the oligonucleotide is also selected from any one of fully defined 20 bp sequences (SEQ ID NO. 207, 209-213, 215, 216, 219, 221-223, 229, 238, 242, 249, 252, 256, 258, 259, 261, 263-268, 270, 271, 274, 275, 277, 278, 286, 294, 306, 311, or 335) given in the specification. The expression is reduced from 90% to 1%. The SNP is selected from polymorphisms identified by Ref SNP rs13114311, rs12506200, rs762855, rs363081, rs363075, rs3025849, rs363102, rs3025838, rs362322, rs2276881, rs1006798, rs3856973, rs2285086, rs7659144, rs16843804, rs2024115, rs10015979, rs7691627, rs4690072, rs6446723, rs363064, rs11731237, rs4690073, rs363099, rs363096, rs2298967, rs2298969, rs6844859, rs363092, rs7685686, rs363088, rs362331, rs916171, rs362275, rs3121419, rs362272, rs362271, rs3775061, rs362310, rs362307, rs362306, rs362303 rs362296, or rs1006798. The differentiating polymorphism is in an intron of HTT or in a promoter of HTT.
- ADMINISTRATION :
Administration can be through subcutaneous, intraperitoneal, intramuscular, intravenous, epidermal, transdermal, mucosal, oral, nasal, rectal, or vaginal route. No dosage details given.
- EXAMPLE :
No suitable example given.

DS - AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LT LU LV MC MK MT NL NO PL PT RO SE SI SK TR OA BW GH GM KE LS MW MZ NA SD SL SZ TZ UG ZM ZW EA LI AL BA RS
PAW - (UYBR) UNIV BRITISH COLUMBIA
INW - CARROLL J; HAYDEN M; WARBY S

12/20 - (C) WPI / Thomson
AN - 2009-M53259 [56]
TI - Use of oligonucleotide comprising inosine and/or uracil and/or nucleotide containing base able to form wobble base pair for preparing medicament for treating or preventing human cis-element repeat instability associated genetic disorders
PN - WO2009099326 A1 20090813 DW200956
AU2009210872 A1 20090813 DW201060
EP2249874 A1 20101117 DW201075
CA2714120 A1 20090813 DW201118
JP2011510678 A 20110407 DW201125
CN101980726 A 20110223 DW201128
INCHENP201005540E E 20110408 DW201128
US2011184050 A1 20110728 DW201149
NZ587178 A 20111125 DW201204

HK1150763 A0 20120113 DW201250
US8263760 B2 20120911 DW201260
PR - EP20080151228 20080208
AB - NOVELTY :
Use of an oligonucleotide comprising inosine and/or uracil and/or nucleotide containing a base able to form a wobble base pair, the oligonucleotide comprising a sequence that is complementary only to a repetitive sequence in a gene transcript for manufacturing a medicament for the treatment or prevention of human cis-element repeat instability associated genetic disorders.
- DETAILED DESCRIPTION :
INDEPENDENT CLAIMS are:
(1) an oligonucleotide comprising an inosine and/or an uracil and/or a nucleotide containing a base able to form a wobble base pair comprising a sequence that is complementary to a repetitive sequence selected from (CAG)n, (GCG)n, (CUG)n, (CGG)n, (GAA)n, (GCC)n and (CCUG)n, and has a length of 9 to 50 nucleotides;
(2) a composition comprising an oligonucleotide and preferably further comprising at least one excipient and/or targeting ligand for delivery of the oligonucleotide to the cell and/or enhancing its intracellular delivery;
(3) a nucleic acid vector, preferably a viral vector, capable of conferring expression of an oligonucleotide in human cells;
(4) an in vitro method for the reduction of repeat containing gene transcripts in a cell comprising the administration of an oligonucleotide or a composition, or a nucleic acid vector; and
(5) an in vitro or ex vivo detection and/or diagnostic method where the oligonucleotide is used.
- USE :
The oligonucleotide is useful for preparing a medicament for treating or preventing human cis-element repeat instability associated genetic disorders (claimed).
- ADVANTAGE :
The invention preferentially targets the expanded repeat transcripts and leaves the transcripts of the normal, wild type allele relatively unaffected.
- BIOTECHNOLOGY :
Preferred Oligonucleotide: In the oligonucleotide, the inosine and/or an uracil and/or a nucleotide containing a base able to form a wobble base pair containing oligonucleotide is a single stranded oligonucleotide. The repetitive element is present in a coding or in a non-coding sequence of the gene transcript. The oligonucleotide comprises or consists of a sequence that is complementary to a repetitive element selected from (CAG)n, (GCG)n, (CUG)n, (CGG)n, (CCG)n, (GAA)n, (GCC)n and (CCUG)n. The oligonucleotide has a length of about 9 to about 50 nucleotides, preferably 12 to 40 nucleotides, more preferably 15 to 30. The oligonucleotide comprises or consists of RNA nucleotides, DNA nucleotides, locked nucleic acid (LNA) nucleotides, peptide nucleic acid (PNA) nucleotides, morpholino phosphorodiamidates, ethylene-bridged nucleic acid (ENA) nucleotides or mixtures with or without a phosphorothioate containing backbone. The oligonucleotide comprises 2'-O-substituted RNA phosphorothioate nucleotides, preferably where the 2'-O-substitution is a methoxy ethyl and/or methyl and/or 2'O,4'C methylene bridge (LNA) and/or 2'O,4'C constrained ethylene (cEt) and/or 2'O, 4'C constrained methoxyethylene (cMOEt). The oligonucleotide comprises a sequence that is complementary only to a repetitive sequence in a gene transcript for the manufacture of a medicament for the treatment or prevention of

human cis-element repeat instability associated genetic disorders and where the oligonucleotide is a RNAse H substantially independent oligonucleotide and preferably where the oligonucleotide has a length of 9 to 50 nucleotides, is substituted in at least one of its 5'or 3'end and comprises less than 9, more preferably less than 6 consecutive deoxyriboses in the rest of its sequence. The oligonucleotide comprises no deoxyribose and the backbone is filly modified. The oligonucleotide in the medicament is provided by a nucleic acid vector capable of conferring expression of the oligonucleotide and/or where the oligonucleotide in the medicament is provided with at least an excipient and/or targeting ligand for delivery of the oligonucleotide to cells and/or enhancing its intracellular delivery. It is preferably provided with a radioactive label or fluorescent label.

- ADMINISTRATION :
Administration can be through intravenous, subcutaneous, intramuscular, intrathecal, and intraventricular routes. No dosage details given.

- EXAMPLE :
No suitable example given.

IC - A61K48/00; A61P21/00; A61P25/00
DS - AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LT LU LV MC MK MT NL NO PL PT RO SE SI SK TR OA BW GH GM KE LS MW MZ NA SD SL SZ TZ UG ZM ZW EA LI AL BA RS
PAW - (PROS-N) PROSENSA HOLDING BV
INW - DE KIMPE J J; PLATENBURG G J

13/20 - (C) WPI / Thomson
AN - 2009-B41569 [15]
TI - New isolated double-stranded short interfering nucleic acid molecule comprises complementary sense and antisense regions, useful for manufacturing a medicament for preventing or treating Huntington's disease

PN - EP2014769	A1	20090114	DW200915
WO2009007855	A2	20090115	DW200915
WO2009007855	A3	20090402	DW200924
EP2014769	B1	20100331	DW201023
CA2690730	A1	20090115	DW201025
DE602007005629E	E	20100512	DW201032
JP2010530239	A	20100909	DW201059
US2010299768	A1	20101125	DW201077
US8217018	B2	20120710	DW201245

PR - EP20070290751 20070618
AB - NOVELTY :
An isolated double-stranded short interfering nucleic acid molecule comprising complementary sense and antisense regions, is new.

- DETAILED DESCRIPTION :
An isolated double-stranded short interfering nucleic acid molecule comprising complementary sense and antisense regions, where the antisense region has 15 to no more than 19 contiguous nucleotides that are complementary to a human huntingtin transcript, the nucleotides are encoded by any of tctggcacacttagtaaca (SEQ ID NO. 1), tcgaaactacctaagatta (SEQ ID NO. 2), and cgtcgaacaggtccaaata (SEQ ID NO. 3), the sense and antisense regions have at least 15 contiguous nucleotides that are complementary to each other and form a duplex, and the double-stranded short interfering nucleic acid molecule inhibits the expression of endogenous wild-type and exogenous human mutated huntingtin genes in cells of a non-human mammal which are

expressing both the huntingtin genes, is new. INDEPENDENT CLAIMS are:
(1) a transcription unit comprising a transcription initiation region, a transcription termination region, and a nucleic acid sequence encoding at least one short interfering nucleic acid molecule, where the nucleic acid sequence is operably linked to the initiation region in a manner that allows expression and/or delivery of the short interfering nucleic acid molecule in a host cell;
(2) an expression vector comprising the transcription unit;
(3) a cell which is modified by the vector; and
(4) a pharmaceutical composition comprising at least one short interfering nucleic acid molecule or an expression vector encoding the short interfering nucleic acid molecule in a carrier.

- ACTIVITY :
Anticonvulsant; Nootropic. No biological data given.
- MECHANISM OF ACTION :
None given.
- USE :
The short interfering nucleic acid molecule is useful for manufacturing medicament for preventing or treating Huntington's disease; and for studying Huntington's disease in a rodent model (all claimed).
- BIOTECHNOLOGY :
Preferred Nucleic Acid: In the double-stranded short interfering nucleic acid molecule above, the sense region comprises at least 15 contiguous nucleotides that are encoded by any of agaccgtgtgaatcattgt (SEQ ID NO. 4), agctttgatggattctaat (SEQ ID NO. 5), and gcagccttgtccaggtttat (SEQ ID NO. 6). It is assembled from two separate oligonucleotides, each of 15 to about 30 nucleotides, to form a duplex structure of at least 15 base pairs. Alternatively, it is assembled from a single oligonucleotide of 31 to about 50 nucleotides, to form a hairpin having a duplex structure of at least 15 base pairs and a loop structure of 4 to 10 nucleotides, where the loop is encoded by ttcaagaga (SEQ ID NO. 7). The double-stranded short interfering nucleic acid molecule is encoded by any of fully defined 47 bp (SEQ ID NO. 8-10) given in the specification. One or both 3' end(s) comprise(s) 1 to about 3 overhanging nucleotides. Both ends are blunt. The double-stranded short interfering nucleic acid molecule is an RNA molecule. It comprises one or more modified pyrimidine and/or purine nucleotides. It further comprises at least one modified internucleotidic linkage. The nonhuman mammal is a mouse or a rat. Preferred Transcription Unit: In the transcription unit above, the transcription initiation region comprises a doxycycline regulated promoter. Preferred Vector: The expression vector is a replication-defective and multiply attenuated lentiviral vector.
- ADMINISTRATION :
Dosage is 0.1-100 mg/kg. Administration can be through systemic, local, oral route, inhalation, or by injection.
- SPECIFIC SEQUENCES :
Specifically claimed are nucleotides that are complementary to a human huntingtin transcript comprising 19-47 bp (SEQ ID NO. 1-10). All sequences are fully defined in the specification. tctggcacacttagtaaca (SEQ ID NO. 1) tcgaaactacctaagatta (SEQ ID NO. 2) cgtcgaacaggtccaaata (SEQ ID NO. 3) agaccgtgtgaatcattgt (SEQ ID NO. 4) agctttgatggattctaat (SEQ ID NO. 5) gcagccttgtccaggtttat (SEQ ID NO. 6) ttcaagaga (SEQ ID NO. 7)
- EXAMPLE :
No suitable example given.

DS - AL AT BA BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT

LU LV MC MK MT NL PL PT RO RS SE SI SK TR BW EA GH GM KE LS MW MZ NA NO OA SD SL SZ TZ UG ZM ZW
PAW - (COMS) COMMISSARIAT ENERGIE ATOMIQUE
INW - DEGLON N; PERRIN V

14/20 - (C) WPI / Thomson
AN - 2008-E48742 [30]
TI - Silencing mRNA encoding mutant huntingtin comprises contacting the cell with RNA silencing agent targeting a heterozygous single nucleotide polymorphism within the target mRNA
PN - WO2008005562 A2 20080110 DW200830
WO2008005562 A3 20081120 DW200879
EP2046993 A2 20090415 DW200926
US2009186410 A1 20090723 DW200950
PR - US20060819704P 20060707; WO2007US15638 20070709; US20090348794 20090105
AB - NOVELTY :
Silencing a target mRNA encoding a mutant huntingtin (htt) protein in a cell comprises contacting the cell with amount of a RNA silencing agent targeting a heterozygous single nucleotide polymorphism (SNP) within the target mRNA, such that RNA silencing of the mRNA occurs, where the SNP has an allelic frequency of at least 35% in a sample population.
- DETAILED DESCRIPTION :
INDEPENDENT CLAIMS are:
(1) an RNA silencing agent comprising an antisense strand comprising 16-25 nucleotides homologous to a region of an mRNA encoding a mutant htt protein, the region comprising a heterozygous SNP having an allelic frequency of at least 35% in a sample population, where the KNA silencing agent is capable of directing RNA silencing of the mRNA; and
(2) an siRNA is selected from an siRNA comprising (i) a sense strand comprising the sequence of SEQ ID NO: 3, 7, 9, or 13 or its variant; and (ii) an antisense strand comprising the sequence of SEQ ID NO: 4, 8, 10, or 14 or its variant, the variant comprising at least one nucleotide analog or backbone modification.
- ACTIVITY :
Anticonvulsant; Nootropic. No biological data given.
- MECHANISM OF ACTION :
Gene Therapy.
- USE :
The method, agent and siRNA are useful for silencing a target mRNA encoding a mutant htt protein in a cell (claimed). Can also be used for treating Huntington's disease.
- BIOTECHNOLOGY :
Preferred Method: In the method above, the SNP is present at genomic site RS362331. The target mRNA comprises the sequence of SEQ ID NO: 5 or 6. The RNA silencing agent is capable of inducing discriminatory RNA silencing. The antisense strand of the RNA silencing agent is complementary to the SNP and where the RNA silencing, agent is capable of substantially silencing the mutant htt protein without substantially silencing the corresponding wild-type htt protein. The sample population is of Western European origin. Silencing a target mRNA encoding a mutant htt protein in a cell comprises contacting the cell with amount of a siRNA targeting a heterozygous SNP within the target mRNA, such that RNA silencing of the mRNA occurs, where the siRNA is the siRNA of (2). The siRNA comprises a lipophilic moiety, i.e. a cholesterol moiety. Preferred RNA Silencing Agent: The RNA silencing agent is capable of inducing discriminatory RNA silencing.

The RNA silencing agent is capable of substantially silencing the mutant htt protein without substantially silencing the corresponding wild-type htt protein. The RNA silencing agent is an siRNA. The siRNA comprises a sense strand having a nucleotide sequence identical to the sequence of the SNP. The sense strand of the siRNA is identical to the polymorphism at a nucleotide position that is 10 nucleotides from the 5' end of the sense strand. The sense strand of the siRNA is identical to the polymorphism at a nucleotide position that is 16 nucleotides from the 5' end of the sense strand.

- ADMINISTRATION :
Dosage is 0.00001-3mg, preferably 0.3-3.0mg, by parenteral, e.g. intravenous, intradermal, subcutaneous, oral (e.g. inhalation), transdermal (topical), transmucosal, or rectal administration.
- EXAMPLE :
No suitable example given.

DS - AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU LV MC MT MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW LI AL BA HR MK RS
PAW - (UMAC) UNIV MASSACHUSETTS
INW - ARONIN N; ZAMORE P; ZAMORE P D

15/20 - (C) WPI / Thomson
AN - 2007-132065 [13]
TI - New nucleic acid molecule suppresses the expression of Macaca mulatta and Homo sapiens mRNA sequences that encode for huntingtin, useful for manufacturing medicament for preventing or treating Huntington's disease
PN - WO2006121960 A2 20061116 DW200713
US2006257912 A1 20061116 DW200713
EP1885854 A2 20080213 DW200813
US2010008981 A1 20100114 DW201005
WO2006121960 A3 20070301 DW201225
US8258112 B2 20120904 DW201259
EP1885854 B1 20121017 DW201268
PR - US20050678729P 20050506; US20060429491 20060504; US20090556888 20090910
AB - NOVELTY :
A nucleic acid molecule comprising a first strand of nucleic acid and a second strand of nucleic acid, where the first strand comprises a nucleotide sequence and the second strand comprises the reverse complement of the nucleotide sequence of the first strand, and where the nucleic acid molecule suppresses the expression of both M. mulatta and H. sapiens mRNA sequences that encode for huntingtin, is new.
- DETAILED DESCRIPTION :
INDEPENDENT CLAIMS are also included for:
(1) an expression cassette comprising a nucleic acid encoding at least one strand of the nucleic acid molecule;
(2) a vector comprising the expression cassette;
(3) a mammalian cell comprising the expression cassette;
(4) a non-human mammal comprising the expression cassette; and
(5) use of the nucleic acid molecule is useful in the manufacture of a medicament for the therapeutic and/or prophylactic treatment of Huntington's disease (HD), where introduction of the medicament into a cell inhibits expression of the huntingtin gene by at least 10%.
- ACTIVITY :
Anticonvulsant; Nootropic. No biological data given.
- MECHANISM OF ACTION :
Gene Therapy.

- USE :
The nucleic acid molecule is useful in the manufacture of a medicament for the therapeutic and/or prophylactic treatment of Huntington's disease, where introduction of the medicament into a cell inhibits expression of the huntingtin gene by at least 10%. The vector is useful in the manufacture of a medicament for the therapeutic and/or prophylactic treatment of Huntington's disease, which further includes providing a M. mulatta or H. sapiens containing a neuronal cell, where the neuronal cell contains the huntingtin gene and the neuronal cell is susceptible to nucleic acid interference, and the huntingtin gene is expressed in the neuronal cell; and contacting the M. mulatta or H. sapiens with the medicament, thus inhibiting expression of the huntingtin gene (all claimed). The nucleic acid sequences and methods can also be used to suppress the expression of Huntington's disease genes encoding for huntingtin protein in primates. It can also be used in the study of the pathogenesis of HD and can also provide a treatment for this disease.
- BIOTECHNOLOGY :
Preferred Nucleic Acid Molecule: The first strand of nucleic acid comprises at least 19 contiguous nucleotides encoded by any of fully defined 19 bp sequences (SEQ ID NO. 1-8) given in the specification, and where the second strand is complementary to at least 15 contiguous nucleotides of the first strand or where the first strand of nucleic acid comprises at least 27 contiguous nucleotides encoded by any of fully defined 27 bp sequences (SEQ ID NO. 9-15) given in the specification, and where the second strand is complementary to at least 23 contiguous nucleotides of the first strand. The first strand is 19-30 base pairs in length. The first and/or the second strand further comprise a 3' overhang region, a 5' overhang region, or both 3' and 5' overhang regions. The first strand and the second strand are operably linked by means of a nucleic acid loop strand to form a hairpin structure comprising a duplex structure and a loop structure. The loop structure contains 4-13 nucleotides. The use above reduces cytotoxic effects of mutant huntingtin in the cell, where the cell is a neuronal cell of a M. mulatta or a H. sapiens. The nucleic acid molecule is introduced using a vector. Preferred Expression Cassette: The expression cassette further comprises an additional feature selected from a promoter, a polyadenylation signal, a marker gene, or its combinations. The promoter is selected from a regulatable promoter, a constitutive promoter, a cytomegalovirus (CMV) promoter, a Rous sarcoma virus (RSV) promoter, a pol II promoter, or a pol III promoter. Preferred Vector: The vector comprises two expression cassettes, a first expression cassette comprising a nucleotide sequence encoding the first strand of the nucleic acid molecule and a second expression cassette comprising a nucleotide sequence encoding the second strand of the nucleic acid molecule. Preferably, the vector is a viral vector. The vector also comprises a promoter. Preparation: No preparation method is given.

IC - A61K31/713; A61K48/00; C12N15/11
DS - AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU LV MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW LI
PAW - (MEDT) MEDTRONIC INC
- (MEDT) MEDTRONIC VIDAMED INC
INW - KAEMMERER W; KAEMMERER W F; KAYTOR M; KAYTOR M D

16/20 - (C) WPI / Thomson
AN - 2007-102417 [10]

TI - New nucleic acid molecules that preferentially suppress expression of amino acid sequences encoding for mutated huntingtin, useful for treating and preventing Huntington's disease

PN - WO2007002904 A2 20070104 DW200710
US2007161590 A1 20070712 DW200748
EP1896586 A2 20080312 DW200820
EP2062980 A2 20090527 DW200935
EP2062980 A3 20090826 DW200956
US2010120900 A1 20100513 DW201032
EP2316967 A1 20110504 DW201129
EP2322657 A1 20110518 DW201133
EP2062980 B1 20110831 DW201156
WO2007002904 A3 20070802 DW201229

PR - US20050695078P 20050628; US20060439858 20060524; US20060478110 20060628; WO2007US12259 20070523; WO2008US64532 20080522; US20090560178 20090915

AB - NOVELTY :
A nucleic acid molecule comprising a nucleotide sequence that preferentially suppresses the expression of amino acid sequences encoding for mutated huntingtin (htt) over suppressing the expression of amino acid sequences encoding for normal htt where nucleotide sequence is a sequence of 19 bp selected from SEQ ID Nos. 1-135, fully defined in the specification, is new.

- DETAILED DESCRIPTION :
INDEPENDENT CLAIMS are also included for:
(1) a method comprising administering to an individual the nucleic acid molecule cited above by targeting an area of a Huntington's disease gene that is heterozygous for the presence of one or more single nucleotide polymorphisms where the individual has been screened for the heterozygous presence of one or more single nucleotide polymorphisms within the individual's Huntington's genes;
(2) a cell comprising the expression cassette;
(3) a vector comprising the expression cassette; and
(4) a kit for screening individuals for the heterozygous presence of one or more single nucleotide polymorphisms within the individual's Huntington's genes.

- ACTIVITY :
Nootropic; Anticonvulsant.
No biological data given.

- MECHANISM OF ACTION :
Gene Therapy.

- USE :
The nucleic acid molecules and methods are useful for preventing or treating symptoms of Huntington's disease.

- BIOTECHNOLOGY :
Preferred Method: In method (1), the nucleic acid molecules are administered to an area selected from the intrathecal space of the spinal cord; the striatum; and/or intracranially. The nucleic acid sequences are administered through an administration system selected from a depot, an infusion pump, an osmotic pump, an interbody pump, and/or a catheter. The nucleic acid sequences are administered through an implanted pump that controls the delivery of the nucleic acid sequences to an area selected as above, where the nucleic acid sequences are delivered in a pharmaceutically effective amount to improve at least one symptom of Huntington's disease.
Preferred Vector: The vector is a viral vector selected from an adenoviral virus vector, a retroviral virus vector, a parvoviral virus vector, a picornaviral virus vector, and a herpes virus vector. The

vector comprises a regulatable or a constitutive promoter operably linked to the nucleic acid sequence.
Preferred Kit: The kit comprises at least one molecular beacon that detects a single nucleotide polymorphism found in a sequence selected from SEQ ID Nos. 1-22, where the molecular beacon comprises at least a portion of the reverse complement of the sequence containing the detected single nucleotide polymorphism. The kit further comprises nucleic acid molecules cited above. The kit further comprises a vector comprising an expression cassette.
- ADMINISTRATION :
The nucleic acid molecules are administered to an area selected from the intrathecal space of the spinal cord; the striatum; intracranially; and their combinations (claimed). No dosage detail is given.
- SPECIFIC SEQUENCES :
Specifically claimed are nucleic acid molecules comprising 19 bp (SEQ ID No. 1-135), fully defined in the specification.
- EXAMPLE :
No suitable example given.

DS - AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU LV MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW LI
PAW - (MEDT) MEDTRONIC INC
INW - JASPERS L; VAN BILSEN P; VAN BILSEN P H J

17/20 - (C) WPI / Thomson
AN - 2007-892884 [82]
TI - Nucleic acid duplex useful for the treatment of e.g. Huntington's disease, comprises two strands of nucleic acid containing specific nucleotides
PN - US2007261126 A1 20071108 DW200782
WO2008021136 A2 20080221 DW200816
WO2008021136 A3 20080703 DW200845
WO2008021136 B1 20080807 DW200854
EP2056881 A2 20090513 DW200932
CN101557831 A 20091014 DW200970
JP2010500025 A 20100107 DW201003
US2010325746 A9 20101223 DW201102
US7902352 B2 20110308 DW201118
PR - US20060501634 20060809; US20060429491 20060504; US20050678729P 20050506
AB - NOVELTY :
An isolated nucleic acid duplex comprises a first strand of nucleic acid and a second strand of nucleic acid, where the first strand comprises at least 19 contiguous nucleotides encoded by the group consisting of SEQ ID NO:1 and SEQ ID NO:4, each containing 19 nucleotides as given in specification and where the second strand is complementary to at least 15 contiguous nucleotides of the first strand.
- DETAILED DESCRIPTION :
INDEPENDENT CLAIMS are included for the following: (1) an expression cassette comprising a nucleic acid encoding at least one strand of the nucleic acid duplex; (2) a vector comprising the expression cassette; (3) a vector (Ve1) comprising two expression cassettes, a first expression cassette comprising a nucleotide sequence encoding the first strand of the nucleic acid duplex and a second expression cassette comprising a nucleotide sequence encoding the second strand of the nucleic acid duplex; (4) a cell comprising the expression cassette; (5) a non-human mammal comprising the expression cassette;

and (6) preventing cytotoxic effects of Huntington's disease (HD) or inhibiting expression of huntingtin in a Macaca mulatta or Homo sapiens involving introducing the isolated nucleic acid duplex into a cell to suppress accumulation of a protein associated with HD, and where the nucleic acid duplex prevents cytotoxic effects of HD.

- ACTIVITY :
Neuroprotective; Nootropic; Anticonvulsant. Test details described but no results given.
- MECHANISM OF ACTION :
Hungtingtin protein expression suppressor.
- USE :
For preventing cytotoxic effects of Huntington's disease (HD) or inhibiting expression of huntingtin in Macaca mulatta or Homo sapiens (claimed).
- ADVANTAGE :
The nucleic acid duplex reduces Huntington's disease (HD) messenger RNA (mRNA) without causing death, anatomical aberrations, alterations in endoplasmic reticulum of the transduced cells, locomotor impairment or cellular alterations of Macaca mulatta or Homo sapiens.
- BIOLOGY :
Preferred Components: The duplex is 19-30 base pairs in length. The first and/or the second strand further comprises an overhang region. The overhang region comprises a 3' overhang region, a 5' overhang region, or both 3' and 5' overhang regions. The overhang region is 1-10 nucleotides in length. The first strand and the second strand are operably linked by means of a nucleic acid loop strand to form a hairpin structure comprising a duplex structure and a loop structure. The nucleic acid duplex, where the loop structure contains 4-10 nucleotides. The expression cassette further comprises a promoter (P1), polyadenylation signal or marker gene. The promoter (P1)is a regulatable promoter or constitutive promoter, such as cytomegalovirus (CMV), Rous sarcoma virus (RSV), polymerase (pol) II or pol III promoter. The polyadenylation signal is a synthetic minimal polyadenylation signal. In vector (Ve1), the first strand comprises SEQ ID. NO: 4. The vector is a viral vector, such as adenoviral, lentiviral, adeno-associated viral (AAV), poliovirus, herpes simplex virus, feline immunodeficiency virus or murine Maloney-based viral vector (preferably adeno-associated viral (AAV) vector). The vector (Ve1) further comprises a promoter (P2). The promoter (P2) is an inducible promoter. The isolated nucleic acid duplex is included within a vector (Ve2). The vector (Ve2) is a viral vector, such as adeno-associated viral (AAV) vector. The cell is a mammalian cell. The non-human mammal is a primate. The Macaca mulatta or Homo sapiens survive for at least four weeks after the step of introducing the nucleic acid complex. The Macaca mulatta or Homo sapiens do not exhibit an impairment in fine locomotor activity. The nucleic acid duplex is introduced into at least one cell located in a brain structure selected from putamen, caudate nucleus, corona radiata or striatum. The expression of the nucleic acid duplex does not impair an endoplasmic reticulum of the at least one cell or does not impair expression or distribution of calnexin; or does not impair expression or distribution of protein disulfide isomerase (PDI).
- ADMINISTRATION :
The dosage of nucleic acid duplex is 0.01-100 nM and is administered locally to basal ganglia, specifically to the caudate nucleus and putamen, intracranially, to intrathecal space of the spinal cord, or administered directly to the brain tissue of the cerebral cortex.
- EXAMPLE :

No suitable example given.
DS - AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU LV MC MT MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW LI AL BA HR MK RS
PAW - (MEDT) MEDTRONIC INC
- (KAEM-I) KAEMMERER W F
- (KAYT-I) KAYTOR M D
INW - KAEMMERER W; KAEMMERER W F; KAYTOR M; KAYTOR M D

18/20 - (C) WPI / Thomson
AN - 2007-752739 [70]
TI - Use of a compound which causes RNA interference, for treating CNS disorder, e.g. dementia, Alzheimer's, Huntington's and/or Parkinson's diseases
PN - WO2007107789 A2 20070927 DW200770
WO2007107789 A3 20080508 DW200835
EP2004823 A2 20081224 DW200903
KR20080111063 A 20081222 DW200914
AU2007228570 A1 20070927 DW200929
CA2645120 A1 20070927 DW200939
CN101448944 A 20090603 DW200940
US2009176728 A1 20090709 DW200945
INCHENP200804860E E 20090313 DW200955
JP2009530257 A 20090827 DW200957
MXPA08011731 A 20090331 DW200966
RU2426544 C2 20110820 DW201156
IL194114 A 20120628 DW201245
PR - GB20060005337 20060317
AB - NOVELTY :
Use of a compound which causes RNA interference in the preparation of a medicament for the effective treatment of a disorder of the CNS, where the medicament is formulated for intranasal administration.
- DETAILED DESCRIPTION :
INDEPENDENT CLAIMS are:
(1) a pharmaceutical composition, for treating CNS disorder, comprising one or more siNA targeting a gene expressed in the CNS or a compound which causes PEA interference in a gene expressed in the CNS, formulated for intranasal administration;
(2) a method for treating a disorder of the CNS; and
(3) a method of reducing expression of a target gene in the CNS of a non-human mammal.
- ACTIVITY :
CNS-Gen; Nootropic; Neuroprotective; Anticonvulsant; Antiparkinsonian.
No biological data given.
- MECHANISM OF ACTION :
Gene Therapy.
- USE :
The compound which causes RNA interference is useful in preparing a medicament for the treatment of a disorder of the CNS, e.g. dementia, Alzheimer's, Huntington's and/or Parkinson's diseases, as well as congenital diseases associated with mutations of genes of the CNS (claimed).
- BIOTECHNOLOGY :
Preferred Compound: The compound causes RNA interference in a gene expressed in the CNS. The compound modulates expression of a target gene with altered levels and/or mutations in a patient in need of treatment, where the target gene is tau, huntingtin, acetylcholinesterase, or a mutated allele of these genes, and where

the compound modulates expression of a mutated allele of the target gene. The target gene expression is modulated in a cell, where the target gene expression is modulated in a cell of the CNS. The compound is siNA, where the siNA is siRNA, dsRNA, or shRNA. The compound modulates miRNA levels. The compound comprises a modified oligonucleotide. The siNA is 40 base pairs or fewer in length. The siNA has 3' overhangs, where the 3' overhangs are dinucleotides, and where the dinucleotide overhangs are made of thymidine nucleotides. Species of compound are used, where the species are targeted to the same or different mRNA species. The compound modulates expression of a target gene involved in dementia, Alzheimer's, Huntington's and/or Parkinson's diseases, or a congenital disease associated with mutations of genes of the CNS. The target gene is tau, where the siNA is targeted against a region nucleotide sequence having a sequence selected from SEQ ID NOS: 1-160 or 161-318. The target gene is huntingtin, acetylcholinesterase, or a mutated allele of a gene selected from tau, huntingtin, or acetylcholinesterase. Preferred Method: Treatment of a disorder of the CNS comprises administering a compound which causes RNA interference intranasally to a patient. Reducing expression of a target gene in the CNS of a non-human mammal comprises intranasally administering a compound which causes KNA interference in the target gene to the non-human mammal. The target gene is expressed at normal levels in the non-human mammal, and the compound is administered for investigation of function of the gene.

- ADMINISTRATION :
The compound is for intranasal administration (claimed). Other routes include systemic, local, oral, transdermal, or by injection. No dosage details given.

- EXAMPLE :
No suitable example given.

IC - C12N15/11

DS - AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU LV MC MT MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW AL BA HR LI MK RS

PAW - (SYLE-N) SYLENTIS SA
- (WILL-I) WILLIAMS G O

INW - ANTON A I J; COMEZ-ACEBO G E; GOMEZ M C J; GOMEZ-ACEBO G E; GOMEZ-ACEBO GULLON E; GULLON E G; JIMENEZ A A I; JIMENEZ ANTON A I; JIMENEZ G M C; JIMENEZ GOMEZ M; JIMENEZ GOMEZ M C; SESTO Y A; SESTO YAGUE A; YAGUE A S

19/20 - (C) WPI / Thomson

AN - 2007-675901 [63]

TI - Treating an individual at risk of suffering or currently suffering from Huntington's Disease (HD) by administering to the individual a pharmaceutical composition comprising an antisense compound

PN - WO2007089584 A2 20070809 DW200763
WO2007089584 A3 20071129 DW200780

PR - US20060836290P 20060807; US20060762954P 20060126

AB - NOVELTY :
Treating an individual at risk of suffering or currently suffering from Huntington's Disease (HD) comprises administering to the individual a pharmaceutical composition comprising an antisense compound that is 12 to 35 nucleobases in length and having at least 90% complementarity to nucleotides 1650-1704, 1807-1874, 3183-3228, 4010-4087, 4265-4288, 4553-4608, 5781-5820 or 6793-6796 of a fully defined 13495-bp sequence (SEQ ID NO: 4).

- ACTIVITY :

Nootropic. No biological data given.
- MECHANISM OF ACTION :
Antisense oligonucleotide inhibitor.
- USE :
The antisense oligonucleotide of 12 to 35 nucleotides comprising at least 12 consecutive nucleotides of a nucleotide sequence consisting of SEQ ID NO. 46-357, 50, 93, 100, 105, 110, 125, 137, 345, 346 or 353 is useful in preparing a medicament for treating an individual at risk of suffering or currently suffering from Huntington's Disease (claimed).
- BIOTECHNOLOGY :
Preferred Method: Treating an individual at risk of suffering or currently suffering from Huntington's Disease (HD) comprises administering to the individual a pharmaceutical composition comprising an antisense compound that is 12 to 35 nucleobases in length and having at least 90 or 95% complementarity to nucleotides 1650-1704, 1807-1874, 3183-3228, 4010-4087, 4265-4288, 4553-4608, 5781-5820 or 6793-6796 of SEQ ID NO: 4. The pharmaceutical composition may comprise an antisense oligonucleotide that is 12 to 35 nucleotides in length comprising at least 12 consecutive nucleotides of a nucleotide sequence consisting of a fully defined sequence comprising 20 (each of the sequences) bp (SEQ ID NO. 46-357). The administering comprises administration into the cerebrospinal fluid of the individual by intrathecal infusion. The treatment comprises improvement in one or more indicators of HD. The treatment comprises increasing the survival time of the individual. The treatment comprises delaying the onset of HD. The antisense compound is an antisense oligonucleotide. The antisense oligonucleotide has at least one modified internucleoside linkage, sugar moiety or nucleobase. The oligonucleotide comprises a chimeric oligonucleotide having a gap segment positioned between 5' and 3' wing segments. The gap segment of the chimeric oligonucleotide comprises 2'-deoxynucleotides and the wing segments are comprised of nucleotides having modified sugar moieties. The modified sugar moiety is 2'-OMe or a bicyclic nucleic acid. The gap segment of the chimeric oligonucleotide consists of ten 2'-deoxynucleotides and each wing segment consists of five 2'-O-methoxyethyl-modified nucleotides. Each internucleoside linkage is a phosphorothioate internucleoside linkage. Each cytosine is a 5-methylcytosine. The method further comprises selecting an individual suffering from HD. The method further comprises selecting an individual susceptible to HD. The compound comprises 17-25, 19-23 or 20 nucleotides. The nucleotide sequence comprises a fully defined sequence comprising 20 (each of the sequences) bp (SEQ ID NO: 50, 93, 100, 105, 110, 125, 137, 345, 346 or 353). The treatment of HD is slowing of HD progression in an individual suffering from HD, preventing the onset of HD in an individual susceptible to HD or increasing survival time of the individual.
- ADMINISTRATION :
The dose comprises 25, 50, 75 or 100 mu g. The composition is administered via intrathecal, intracerebroventricular or intraparenchymal route (claimed).
- EXAMPLE :
No suitable example given.

DS - AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU LV MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW

PAW - (ISSP) ISIS PHARM INC
- (CHDI-N) CHDI INC

INW - HUNG G; LEEDS J

20/20 - (C) WPI / Thomson
AN - 2007-620505 [59]
TI - New double-stranded ribonucleic acid, useful for treating, preventing or managing Huntingtons disease
PN - US2007099860 A1 20070503 DW200759
WO2007051045 A2 20070503 DW200759
US7320965 B2 20080122 DW200807
EP1941059 A2 20080709 DW200847
AU2006305886 A1 20070503 DW200858
CN101365801 A 20090211 DW200919
JP2009513144 A 20090402 DW200926
CA2627025 A1 20070503 DW200929
AU2006305886B B2 20101118 DW201077
AU2010241477 A1 20101209 DW201104
WO2007051045 A3 20070726 DW201229
PR - US20060588674 20061027; US20060836040P 20060807; US20060819038P 20060707; US20050731555P 20051028; US20060588674 20061027; AU20100241477 20101116
AB - NOVELTY :
A double-stranded ribonucleic acid (dsRNA) for inhibiting the expression of a human Huntington gene (HD gene) in a cell, where the dsRNA comprises at least two sequences that are complementary to each other and where a sense strand comprises a first sequence and an antisense strand comprises a second sequence comprising a region of complementarity which is substantially complementary to at least a part of a mRNA encoding HD, and where the region of complementarity is less than 30 nucleotides in length and where the dsRNA inhibits expression of the HD gene by at least 20 %, is new.
- DETAILED DESCRIPTION :
INDEPENDENT CLAIMS are:
(1) a pharmaceutical composition for inhibiting the expression of the HD gene in an organism, comprising a dsRNA above and a pharmaceutical carrier;
(2) a method for inhibiting the expression of the HD gene in a cell;
(3) a method of treating, preventing or managing HD;
(4) a vector, for inhibiting the expression of the HD gene in a cell, comprising a regulatory sequence operably linked to a nucleotide sequence that encodes at least one strand of a dsRNA above; and
(5) a cell comprising the dsRNA or the vector above.
- ACTIVITY :
Anticonvulsive; Nootropic. No biological data given.
- MECHANISM OF ACTION :
Gene therapy.
- USE :
The dsRNA, composition, and method are useful for treating, preventing or managing Huntington's disease.
- BIOTECHNOLOGY :
Preferred dsRNA: The first or second sequence is selected from Tables 1, 2 (preferred), 7, 8 or 10 given in the specification. The dsRNA comprises at least one modified nucleotide selected from 2'-O-methyl modified nucleotide, nucleotide comprising a 5'-phosphorothioate group, or terminal nucleotide linked to a cholesteryl derivative or dodecanoic acid bisdecylamide group. The modified nucleotide is 2'-deoxy-2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an abasic nucleotide, 2'-amino-modified nucleotide, 2'-alkyl-modified nucleotide, morpholino nucleotide, a phosphoramidate, or a non-natural base comprising

nucleotide.
Preferred Method: Inhibiting the expression of the HD gene in a cell comprises introducing into the cell a dsRNA above and maintaining the produced cell for a time to obtain degradation of the mRNA transcript of the HD gene, thus inhibiting expression of the HD gene in the cell. Treating, preventing or managing Huntingtin disease comprises administering to a patient in need of such treatment, prevention or management a therapeutic or prophylactic amount of a dsRNA above.
- ADMINISTRATION :
Administration is by oral or parenteral including intracranial (including intraparenchymal and intraventricular), intrathecal, epidural, intravenous, intramuscular, intraperitoneal, subcutaneous, transdermal, airway (aerosol), nasal, rectal, vaginal, or topical (including buccal and sublingual) routes. No dosage details given.
- EXAMPLE :
No suitable example given.

DS - AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU LV MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW LI

PAW - (ALNY-N) ALNYLAM PHARM INC
- (BRAM-I) BRAMLAGE B
- (BUMC-I) BUMCROT D
- (HADW-I) HADWIGER P
- (ROEH-I) ROEHL I
- (SAHD-I) SAH D W
- (TANP-I) TAN P
- (VORN-I) VORNLOCHER H

INW - BRAMLAGE B; BUMCROT D; HADWIGER P; ROEHL I; SAH D W; TAN P; VORNLOCHER H

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D) Base de Datos INVENES

1/3. INTERFERENCIA DE ARN ESPECIFICO DE ALELOS.

Número de Publicación: ES2334125 T3 (05.03.2010)

También publicado como: EP1567539 A2 (31.08.2005)
EP1567539 A4 (26.07.2006)
EP1567539 B1 (23.09.2009)
WO2004042027 A2 (21.05.2004)
WO2004042027 A3 (15.07.2004)

Número de Solicitud: PCT/US2003/035009 (04.11.2003)
E03783121 (04.11.2003)

Número de Prioridad: US20020423507P (04.11.2002)
US20030488283P (18.07.2003)

Solicitante: UNIVERSITY OF MASSACHUSETTS (US)
ONE BEACON STREET, 26TH FLOOR,BOSTON, MA 02108

Inventor/es: XU, ZUOSHANG (US);
ZAMORE, PHILLIP, D.;

CIP: ***A61K31/713*** *(2006.01)* ***A61K48/00*** *(2006.01)* ***C12N5/02*** *(2006.01)*
C12N15/113 *(2010.01)*
A61K38/00 (2006.01)

Clasificación Europea: C12N15/113D C12Y115/01001

Resumen: Un procedimiento *ex vivo* para inhibir selectivamente la expresión de un alelo objetivo mutante de un gen SOD1 en una célula que comprende alelos de tipo salvaje y mutantes del gen, en donde el alelo objetivo comprende una mutación puntual correlacionada con la esclerosis lateral amiotrófica, el procedimiento comprende administrar a la célula un siARN específico para la mutación puntual de tal modo que ocurre la interferencia de ARN específica de alelos del alelo objetivo mutante y se preserva la expresión del alelo de tipo salvaje, en donde el siARN es apareado completamente con un mARN mutante codificado por el alelo mutante pero forma un mal apareamiento de un solo nucleótido con un mARN de tipo salvaje codificado por el alelo de tipo salvaje.

2/3. RNADE INTERFERENCIA UTILES PARA LA ELABORACION DE MEDICAMENTOS PARA EL TRATAMIENTO O PREVENCION DE ENFERMEDADES HUMANAS NEURODEGENERATIVAS,MEDICAMENTOS ASI OBTENIDOS Y SUS APLICACIONES

Número de Publicación: ES2352925 A1 (24.02.2011)

También publicado como: ES2352925 B1 (02.01.2012)

Número de Solicitud: P200930454 (14.07.2009)

Solicitante: CONSEJO SUPERIOR DE INVESTIGACIONES CIENTIFICAS (CSIC) (ES)
C/ SERRANO, 117 E-28006 MADRID, España

Inventor/es: ABAD FERNANDEZ, MARIA ALBA;
ENGUITA MARTINEZ, MARTA;
TRULLAS OLIVA, RAMON;

CIP: ***C12N15/11*** *(2006.01)* ***A61K48/00*** *(2006.01)* ***A61P25/28*** *(2006.01)*

Documentos citados: (X) LNP
(X) WO0136626 A2
(A) LNP

Resumen: RNA de interferencia útiles para la elaboración de medicamentos para el tratamiento o prevención de enfermedades humanas neurodegenerativas, medicamentos así obtenidos y sus aplicaciones.

La presente invención describe inhibidores de la expresión génica del gen que codifica para la proteína NP1, que actúa como un inductor de apoptosis neural y neurodegeneración, útiles para la elaboración de medicamentos o composiciones farmacéuticas para el tratamiento o prevención de enfermedades humanas neurológicas, preferentemente enfermedades neurodegenerativas. Más preferentemente, la enfermedad neurodegenerativa es el Alzheimer. Estos inhibidores incluyen RNAi que actúan silenciando la expresión génica del gen NP1.

3/3. RNA DE INTERFERENCIA UTILES PARA LA ELABORACION DE MEDICAMENTOS PARA EL TRATAMIENTO O PREVENCION DE ENFERMEDADES HUMANAS NEURODEGENERATIVAS, MEDICAMENTOS ASI OBTENIDOS Y SUS APLICACIONES

Número de Publicación: ES2352630 A1 (22.02.2011)

También publicado como: ES2352630 B1 (02.01.2012)

Número de Solicitud: P200930455 (14.07.2009)

Solicitante: CONSEJO SUPERIOR DE INVESTIGACIONES CIENTÍFICAS (CSIC) (ES)
C/ SERRANO, 117 E-28006 MADRID, España

Inventor/es: ABAD FERNANDEZ, MARIA ALBA;
ENGUITA MARTINEZ, MARTA;
TRULLAS OLIVA, RAMON;

CIP: ***C12N15/11*** *(2006.01)* ***A61K48/00*** *(2006.01)* ***A61P25/28*** *(2006.01)*

Documentos citados: (X) LNP
(X) WO0136626 A2
(X) LNP

Resumen: RNA de interferencia útiles para la elaboración de medicamentos para el tratamiento o prevención de enfermedades humanas neurodegenerativas, medicamentos así obtenidos y sus aplicaciones.

La presente invención describe inhibidores de la expresión génica del gen que codifica para la proteína NP1, que actúa como un inductor de apoptosis neural y neurodegeneración, útiles para la elaboración de medicamentos o composiciones farmacéuticas para el tratamiento o prevención de enfermedades humanas neurológicas, preferentemente enfermedades neurodegenerativas. Más preferentemente, la enfermedad neurodegenerativa es el Alzheimer. Estos inhibidores incluyen RNAi que actúan silenciando la expresión génica del gen NP1.

ANEXO 2. Bases de datos utilizadas en la búsqueda

BIOSIS
Productor: *Biosis, U.S.A.*
Contenido: *Información bibliográfica mundial sobre todas las áreas de las ciencias biológicas y biomédicas desde 1969.*
Actualización: *Semanal*
Número de documentos: *más de 14.000.000 de registros*

EBI *(Bases de datos de secuencias biológicas EMBL/GenBank/DDBJ)*
Productor: *European Bioinforamtics Institute*
Contenido: *EMBL, GenBanK y DDBJ intercambian datos nuevos y actualizados diariamente con el objetivo de alcanzar una sincronización óptima. Como resultado de este intercambio las tres bases contienen exactamente la misma información salvo par aquellas secuencias que hayan sido añadidas en las últimas 24 horas.*
Actualización: *Diaria*

EMBASE *(Literatura no patente en el campo de las ciencias biomédicas y la farmacología)*
Productor: *Elsevier Science B.V.*
Contenido: *4000 revistas científicas de 70 países en el campo de las ciencias biomédicas y la farmacología*
Actualización: *Semanal*
Número de documentos: *más de 9.000.000 de registros*

EPODOC
Productor: *Oficina Europea de Patentes (O.E.P.)*
Contenido: *Documentos de patente que forman parte de la documentación sistemática de búsqueda de la O.E.P.*
Actualización: *Semanal*
Número de documentos: *aproximadamente 58.000.000*

INVENES
Productor: *Oficina Española de Patentes y Marcas*
Contenido: *Patentes y Modelos de Utilidad españoles desde 1968 hasta la fecha y solicitudes de patentes europeas y PCT que designan España que generan un documento en español.*
Actualización: *Quincenal*
Número de documentos: *aproximadamente 670.000 referencias bibliográficas y 630.000 documentos completos*

MEDLINE *(MEDical Literature Analysis and Retrieval System OnLINE)*
Productor: *U.S. National Library of medicine (NLM)*
Contenido: *Información bibliográfica mundial sobre todas las áreas de las ciencias biomédicas desde 1966.*
Actualización: *Semanal*
Número de documentos: *más de 11.000.000 de registros*

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NPL *((Non Patent Literature))*
Productor: *Oficina Europea de Patentes (O.E.P.)*
Contenido: *Datos bibliográficos de documentos de literatura no patente que forman parte de la documentación de búsqueda de la O.E.P.*
Actualización: *Semanal*
Número de documentos: *aproximadamente 1.900.000*

WPI *(World Patents Index)*
Productor: *Thomson*
Contenido: *Datos bibliográficos de solicitudes publicadas y patentes concedidas por 40 oficinas de patentes desde 1963 hasta la fecha, además de patentes europeas y PCT, desde 1981.*
Actualización: *Semanal (20.000 documentos/semana)*
Número de documentos: *aproximadamente 15.000.000*

XPESP
Productor: *Elsevier Science Publications*
Contenido: *Literatura no patente desde 1.994 sobre un amplio rango de sectores técnicos relacionados con la Física, Electricidad, Mecánica y Química.*
Actualización: *Quincenal*
Número de documentos: *más de 519.894 documentos*

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ANEXO 3. Códigos de las bases de datos

BIOSIS

AB	:	Resumen
AN	:	Número de acceso
AU	:	Autor
AUAF	:	Centro de investigación
CONF	:	Conferencia
ED	:	Editor
IN	:	Inventor
IRN	:	Número de registro Internacional
NR	:	Número de edición
PA	:	Solicitante
PG	:	Páginas
PN	:	Número de patente
PUB	:	Datos de Publicación
TI	:	Título
VOL	:	Volumen

MEDLINE

AB	:	Resumen
AN	:	Número de acceso
AU	:	Autor
AW	:	Nombre de sustancia
DT	:	Tipo de documento
IRN	:	Número de registro internacional
IW	:	Términos indexados
LA	:	Idioma
NR	:	Número de edición
PG	:	Números de páginas
PUB	:	Datos de publicación
TI	:	Título
VOL	:	Volumen

EPODOC

AB	:	Resumen
AP	:	Datos de solicitud
CT	:	Documentos citados en el informe de búsqueda
CTNP	:	Literatura no patente citada en el informe de búsqueda
EC	:	Clasificación europea de Patentes
IC	:	Clasificación Internacional de Patentes
ICO	:	Códigos de indexación
PAW	:	Solicitante
PN	:	Número y fecha de publicación
PR	:	Número y fecha de prioridad
TI	:	Título

WPI

AB	:	Resumen
AN	:	Número de acceso Derwent
CT	:	Patentes citadas en el Informe de Búsqueda
DN	:	Estados designados (vía nacional)
DS	:	Estados designados (vía regional)
IC	:	Clasificación Internacional de Patentes
INW	:	Inventor
PAW	:	Solicitante
PN	:	Números y fechas de publicación
PR	:	Números y fechas de prioridad
TI	:	Título

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ANEXO 4. Abreviaturas de países

AE	:	Emiratos Árabes Unidos
AG	:	Antigua y Barbuda
AL	:	Albania
AM	:	Armenia
AP	:	Patentes ARIPO
AR	:	Argentina
AT	:	Austria
AU	:	Australia
AZ	:	Azerbayán
BA	:	Bosnia y Herzegovina
BB	:	Barbados
BE	:	Bélgica
BF	:	Burkina Faso
BG	:	Bulgaria
BJ	:	Benin
BO	:	Bolivia
BR	:	Brasil
BW	:	Botswana
BY	:	Bielorrusia
BZ	:	Belice
CA	:	Canadá
CF	:	Rep. Centroafricana
CG	:	Congo
CH	:	Suiza
CI	:	Costa de Marfil
CL	:	Chile
CM	:	Camerún
CN	:	China
CO	:	Colombia
CR	:	Costa Rica
CS	:	Checoslovaquia
CU	:	Cuba
CY	:	Chipre
CZ	:	Rep. Checa
DD	:	Rep. Dem. Alemana
DE	:	Alemania
DK	:	Dinamarca
DM	:	Dominica
DZ	:	Argelia
EA	:	Patente Euroasiática
EC	:	Ecuador
EE	:	Estonia
EG	:	Egipto
EP	:	Patente Europea
ES	:	España
FI	:	Finlandia
FR	:	Francia
GA	:	Gabón
GB	:	Reino Unido
GD	:	Granada
GE	:	Georgia
GH	:	Ghana
GM	:	Gambia
GN	:	Guinea
GQ	:	Guinea Ecuatorial
GR	:	Grecia
GW	:	Guinea-Bissau
HR	:	Croacia
HU	:	Hungría
ID	:	Indonesia
IE	:	Irlanda
IL	:	Israel
IN	:	India
IS	:	Islandia
IT	:	Italia
JP	:	Japón
KE	:	Kenia
KG	:	Kirguizistán
KP	:	Rep. Pop. Dem. Corea
KR	:	Rep. Corea
KZ	:	Kazajstán
LC	:	Santa Lucía
LI	:	Liechtenstein
LK	:	Sri Lanka
LR	:	Liberia
LS	:	Lesoto
LT	:	Lituania
LU	:	Luxemburgo
LV	:	Letonia
MA	:	Marruecos
MC	:	Mónaco
MD	:	Rep. Moldavia
MG	:	Madagascar
MK	:	Rep. Macedonia
ML	:	Mali
MN	:	Mongolia
MR	:	Mauritania
MW	:	Malaui
MX	:	México
MZ	:	Mozambique
NA	:	Namibia
NE	:	Níger
NI	:	Nicaragua
NL	:	Países Bajos
NO	:	Noruega
NZ	:	Nueva Zelanda
OA	:	Patente OAPI
OM	:	Oman
PG	:	Papua Nueva Guinea
PH	:	Filipinas
PL	:	Polonia
PT	:	Portugal
RO	:	Rumania
RU	:	Federación Rusa
SC	:	Seychelles
SD	:	Sudán
SE	:	Suecia
SG	:	Singapur
SI	:	Eslovenia
SK	:	Eslovaquia
SL	:	Sierra Leona
SN	:	Senegal
SU	:	Unión Soviética
SY	:	Rep. Árabe Siria
SZ	:	Suazilandia
TD	:	Chad
TG	:	Togo
TJ	:	Tayikistán
TM	:	Turkmenistán
TN	:	Túnez
TR	:	Turquía
TT	:	Trinidad y Tobago
TW	:	Taiwán
TZ	:	Rep. Unida de Tanzania
UA	:	Ucrania
UG	:	Uganda
US	:	Estados Unidos
UZ	:	Uzbekistán
VC	:	San Vicente y las Granadinas
VE	:	Venezuela
VN	:	Vietnam
WO	:	Patente PCT
YU	:	Yugoslavia / Serbia y Montenegro
ZA	:	Sudáfrica
ZM	:	Zambia
ZR	:	Zaire
ZW	:	Zimbabue

ANEXO 5. Glosario de términos de propiedad industrial

ACTIVIDAD INVENTIVA:

Requisito de patentabilidad, junto con la novedad y la aplicación industrial. Significa que la invención ha de ser no sólo nueva, sino también no obvia, en el sentido de que, teniendo en cuenta el estado de la técnica, no resulte evidente para un experto en la materia (especialista en el campo técnico correspondiente).

APLICACIÓN INDUSTRIAL:

Requisito de patentabilidad, junto con la novedad y la actividad inventiva. Se entiende que una invención es susceptible de aplicación industrial cuando su objeto puede ser fabricada o utilizado en cualquier clase de industria, incluida la agrícola.

CLASIFICACIÓN INTERNACIONAL DE PATENTES (CIP):

Sistema de clasificación jerárquica utilizado para la clasificación y búsqueda de los documentos de patente (solicitudes de patentes, patentes concedidas, modelos de utilidad, etc.).También se utiliza como instrumento para ordenar los documentos de patente, como base para la difusión selectiva de información y para el estudio del estado de la técnica en un campo dado de la tecnología. El esquema de la clasificación contiene 70,000 entradas. La oficina Europea de patentes dispone de su propio esquema de clasificación basado en la CIP, denominado Clasificación Europea de Patentes (ECLA).

DERECHO DE PRIORIDAD:

Este es un derecho basado en el Convenio de la Unión de París (CUP), para la protección de la propiedad industrial (París, 20/3/1883), que afecta a los Estados que forman parte de este Convenio (en la actualidad casi un centenar, entre los que figura España)(Instrumento de ratificación de España de 13/12/71 al Acta de Estocolmo de 14/7/67, modificativa del CUP; BOE nº 28, 1/2/74). Este derecho significa que, en base a la fecha de una primera solicitud regular depositada en uno de los Estados contratantes, el solicitante dispone de un periodo de doce meses para solicitar protección en otros Estados contratante mediante solicitudes posteriores en las que se invocará la prioridad de la primera solicitud. El efecto que produce es que todas las solicitudes posteriores se consideran como depositadas en la fecha de la primera, es decir, tendrán "prioridad" sobre las solicitudes presentadas por otras personas para la misma invención en el periodo intermedio entre la fecha del primer depósito y las fecha posteriores de presentación en las distintas oficinas nacionales. La fecha del primer depósito es por lo tanto la que se tendrá en cuenta para delimitar el Estado de la Técnica anterior cuando se realice el examen sustantivo de la solicitud. La ventaja principal es que permite disponer al solicitante de un plazo de doce meses para decidir en qué países desea solicitar protección, sin necesidad de presentar todas las solicitudes al mismo tiempo.

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ESTADO DE LA TÉCNICA: *(state of the art, prior art).*

Se refiere al nivel de desarrollo alcanzado por un área particular de una materia técnica en una fecha dada. Está constituida por todo lo que antes de esta fecha se ha hecho accesible al público en cualquier parte del mundo y por cualquier medio (descripción escrita, oral, uso, etc.). Para una invención dada, el estado de la técnica es decisivo para la determinación del cumplimiento de los requisitos de patentabilidad en cuanto a novedad y actividad inventiva. La fecha que delimita este estado es la de presentación de la solicitud, que será la de prioridad en los casos correspondientes.

FAMILIA DE PATENTES:

En general, se denomina familia de patentes a los documentos de patente publicados en diferentes países pero relacionados con la misma invención. Para los países miembros del Convenio de la Unión de París (ver derecho de prioridad), estos documentos pueden ser identificados normalmente a través de los datos de la primera solicitud en base a la cual se invoca el derecho de prioridad en las solicitudes posteriores. Esta primera solicitud suele denominarse patente prioritaria. Cada "miembro" de la familia describe la misma invención pero a menudo en diferentes idiomas.

INFORME SOBRE EL ESTADO DE LA TÉCNICA: *(search report).*

Es un informe que contiene los resultados de la búsqueda en el estado de la técnica, citando los documentos que se consideran relevantes para determinar, en particular, la novedad o actividad inventiva de una invención determinada, de acuerdo a lo que se reivindica en la solicitud objeto de informe. Son realizados por las Oficinas de Propiedad Industrial de acuerdo a la legislación propia de cada país u organización regional.

MODELO DE UTILIDAD:

Según la Ley de Patentes española (Ley 11, 20/3/86; BOE nº 73, 26/3/86), son protegibles en España como modelos de utilidad las invenciones que, siendo nuevas e implicando una actividad inventiva, consisten en dar a un objeto una configuración, estructura o constitución de la que resulte alguna ventaja prácticamente apreciable para un uso o fabricación. En particular pueden protegerse como modelos de utilidad los utensilios, instrumentos, herramientas, aparatos, dispositivos o partes de los mismo, que reúnan los requisitos enunciados anteriormente. El estado de la técnica con referencia al cual debe juzgarse la novedad y la actividad inventiva de las invenciones protegibles como modelos de utilidad, está constituido por todo aquello que antes de la fecha de presentación de la solicitud de protección como modelo ha sido divulgado en España, por una descripción escrita u oral, por una utilización o por cualquier otro medio. Para su protección como modelo de utilidad se considera que una invención implica una actividad inventiva si no resulta del estado de la técnica de una manera muy evidente para un experto en la materia.

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NOVEDAD:

Requisito de patentabilidad, junto con la actividad inventiva y la aplicación industrial. Se considera que una invención es nueva cuando no está comprendida en el estado de la técnica (ver estado de la técnica, actividad inventiva y aplicación industrial).

PATENTE:

Según la Ley de Patentes española (Ley 11, 20/3/86; BOE nº 73, 26/3/86), son protegibles en España como patentes las invenciones nuevas que impliquen una actividad inventiva y sean susceptibles de aplicación industrial.

No se considerarán invenciones, en el sentido del apartado anterior, en particular:

a) Los descubrimientos, las teorías científicas y los métodos matemáticos.

b) Las obras literarias o artísticas o cualquier otra creación estéticas, así como las obras científicas.

c) Los planes, reglas y métodos para el ejercicio de actividades intelectuales, para juegos o para actividades económico-comerciales, así como los programas de ordenador.

d) Las formas de presentar informaciones.

No se considerarán como invenciones susceptibles de aplicación industrial los métodos de tratamiento quirúrgico o terapéutico del cuerpo humano o animal, ni los métodos de diagnóstico aplicados al cuerpo humano o animal. Esta disposición no será aplicable a los productos, especialmente a las sustancias o composiciones ni a las invenciones de aparatos o instrumentos para la puesta en práctica de tales métodos.

Se considera que una invención es nueva cuando no está comprendida en el estado de la técnica, que está constituido por todo lo que antes de la fecha de presentación de la solicitud de patente se ha hecho accesible al público en España o en el extranjero por una descripción escrita u oral, por una utilización o por cualquier otro medio.

Se considera que una invención implica una actividad inventiva si aquella no resulta del estado de la técnica de una manera evidente para un experto en la materia.

PATENTE EUROPEA:

Patente tramitada por la Oficina Europea de Patentes en virtud del CPE [Convenio de Patentes Europeas, Munich, 5/10/73; (Instrumento de Adhesión de España de 10/7/86; BOE nº 234, 30/9/86)] y que permite al inventor, mediante una única solicitud de patente depositada en dicha Oficina, obtener protección en todos y cada uno de los países miembros del Convenio que hayan sido designados por él. Una vez concedida, la patente europea se divide en un haz de patentes nacionales,

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sometidas a la legislación del país respectivo. En la actualidad son miembros de CPE los siguientes 31 países: Alemania, Austria, Bélgica, Bulgaria, Chipre, Dinamarca, Eslovaquia, Eslovenia, Estonia, España, Estonia, Finlandia, Francia, Grecia, Hungría, Irlanda, Italia, Latvia, Liechtenstein, Lituania, Luxemburgo, Mónaco, Países Bajos, Polonia, Portugal, Reino Unido, Rumania, República Checa, Suecia, Suiza y Turquía.

PATENTE PCT:

*Patente tramitada en virtud del Tratado de Cooperación en Materia de Patentes (**P**atent **C**ooperation **T**reaty, Washington, 19/6/70)(Instrumento de Adhesión de España de 13/7/89; BOE nº 267, 7/11/89), que permite al inventor, mediante una única solicitud de patente, solicitar protección en todos los países designados por él, de los adheridos al Tratado. España se adhirió inicialmente al Capítulo I, en el que se señala que se realizará un informe de búsqueda por una de las Oficinas establecidas por el tratado como Autoridad Internacional de Búsqueda, informe que posteriormente es enviado a las correspondientes oficinas nacionales de los países designados donde se estudia si se concede o deniega la patente de acuerdo con cada una de las legislaciones nacionales. El 6 de junio de 1997, España levantó la reserva al Capítulo II del Tratado, por lo que a partir del 6 de septiembre de 1997 (BOE nº 36, 11/2/98) los españoles o residente en nuestro país pueden presentar solicitudes de examen preliminar internacional para sus solicitudes PCT. En la actualidad forman parte del Tratado 132 países (ver Anexo 4).*

VÍA EURO-PCT:

Se refiere a la vía que siguen las solicitudes de patente PCT que designan los países europeos firmante del Convenio de la Patente Europea (CPE) a través de una patente europea. Así, la primera parte del procedimiento, hasta la publicación de la solicitud y del informe de búsqueda (search report). se realiza como una solicitud PCT. A partir de ahí, y a petición del solicitante, se entra en la vía de la patente europea, publicándose de nuevo la solicitud en el caso en que la solicitud original no esté redactada en alguno de los tres idiomas oficiales del CPE (inglés, francés o alemán). En caso contrario, la solicitud no se publica de nuevo, pero se le otorga una fecha de publicación de la solicitud europea y se continúa la tramitación por parte de la Oficina Europea de Patentes hasta su concesión o denegación, siendo el procedimiento idéntico al de cualquier otra solicitud europea.

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