



(12) **United States Patent**  
**Fire et al.**

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- (54) **GENETIC INHIBITION BY DOUBLE-STRANDED RNA**
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5,107,065 A	4/1992	Shewmaker
5,190,931 A	3/1993	Inouye
5,208,149 A	5/1993	Inouye
5,258,369 A	11/1993	Carter
5,272,065 A	12/1993	Inouye
5,365,015 A	11/1994	Grierson et al.
5,453,566 A	9/1995	Shewmaker
5,738,985 A	4/1998	Miles
5,795,715 A	8/1998	Livache
5,874,555 A	2/1999	Dervan
5,972,704 A *	10/1999	Draper et al.
6,010,908 A	1/2000	Gruenert et al.
6,136,601 A	10/2000	Meyer, Jr. et al.

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Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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- (51) **Int. Cl.<sup>7</sup>** ..... **C12Q 1/68; C12N 15/85**
- (52) **U.S. Cl.** ..... **435/6; 435/91.1; 435/325**
- (58) **Field of Search** ..... **514/44; 435/6, 435/91.1, 325**

(56) **References Cited**

**U.S. PATENT DOCUMENTS**

4,469,863 A	9/1984	Ts'o et al.
4,511,713 A	4/1985	Miller et al.
5,034,323 A	7/1991	Jorgensen et al.

**FOREIGN PATENT DOCUMENTS**

WO	94/01550	* 1/1994
WO	WO 99/32619	7/1999
WO	WO 99/53050	10/1999
WO	WO 99/61631	12/1999
WO	WO 00/01846	1/2000
WO	WO 00/63364	10/2000

**OTHER PUBLICATIONS**

Sharp, 1999. *Genes and Development*, 13:139-141.\*  
 Clemens. et al., May 23, 2000. *Proc Natl Acad Sci*, early edition,  
<http://www.pnas.org/cgi/doi/10.1073/pnas.110149597>.\*

(List continued on next page.)

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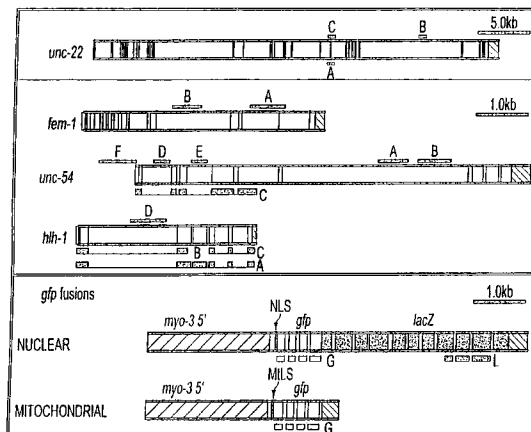
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(57) **ABSTRACT**

A process is provided of introducing an RNA into a living cell to inhibit gene expression of a target gene in that cell. The process may be practiced ex vivo or in vivo. The RNA has a region with double-stranded structure. Inhibition is sequence-specific in that the nucleotide sequences of the duplex region of the RNA and of a portion of the target gene are identical. The present invention is distinguished from prior art interference in gene expression by antisense or triple-strand methods.

**22 Claims, 5 Drawing Sheets**



## OTHER PUBLICATIONS

- Verma et al. *Nature*, vol. 389, pp. 239–242, Sep. 1997.\*
- Anderson, *Nature*, vol. 392, pp. 25–30, Apr. 1998.\*
- Branch, *TIBS* 23, pp. 45–50, Feb. 1998.\*
- Agrawal, *TIBTech*, vol. 14, pp. 376–387, Oct. 1996.\*
- Mercola et al, *Antisense Approaches to Cancer Gene Therapy*, 1995, *Cancer Gene Therapy*, vol. 2, No. 1, pp. 47–59.\*
- Montgomery, M., and Fire, A. (1998) Double-stranded RNA as a mediator in sequence-specific genetic silencing and co-suppression. *Trends in Genetics* 14: 255–258.
- Harfe, B., et al. (1998) Analysis of a *Caenorhabditis elegans* twist homolog identifies conserved and divergent aspects of mesodermal patterning. *Genes and Development* 12: 2623–2635.
- Tabara, H., et al. (1998) RNAi in *C. elegans*: Soaking in the genome sequence. *Science* 282: 430–431.
- Timmons, L., and Fire, A. (1998) Specific interference by ingested dsRNA. *Nature*, 395: 854.
- Montgomery, M.K., et al., (1998) RNA as a target of double-stranded RNA-mediated genetic interference in *Caenorhabditis elegans*. *Proc. Natl. Acad. Sci.* 95:15502–15507.
- Fire, A., et al., (1991) Production of antisense RNA leads to effective and specific inhibition of gene expression in *C. elegans* muscle. *Development* 113:503–514.
- Grieson, D. et al., (1991) Does co-suppression of sense genes in transgenic plants involve antisense RNA? *Trends in Biotechnology* 9:122–123.
- Nellen, W., and Lichtenstein, C. (1993) What makes an mRNA anti-sensitive? *Trends in Biochemical Sciences* 18: 419–423.
- Guo, S. and Kemphues, K. (1995) par-1, a gene required for establishing polarity in *C. elegans* embryos, encodes a putative Ser/Thr kinase that is asymmetrically distributed. *Cell* 81:611–620.
- Matzke, M.A., and Matzke, A.J.M. (1995) How and why do plants inactivate homologous (trans)genes? *Plant Physiology* 107: 679–685.
- Metzlaff, M., et al., (1997) RNA-mediated RNA degradation and chalcone synthetase A silencing in petunia. *Cell* 88: 845–854.
- Ratcliff, F., et al., (1997) A similarity between viral defense and gene silencing in plants. *Science* 276: 1588–1560.
- Jorgensen, R.A., et al., (1998) An RNA-based information superhighway in plants. *Science* 279: 1486–1487.
- Waterhouse, P.M., et al., (1998) Virus resistance and gene silencing in plants can be induced by simultaneous expression of sense and antisense RNA. *Proc. Natl. Acad. Sci.* 95: 13959–13964.
- Ngô, H., et al., (1998) Double-stranded RNA induces mRNA degradation in *Trypanosoma brucei*. *Proc. Natl. Acad. Sci.* 95: 14687–14692.
- Kennerdell, J., and Carthew, R. (1998) *Drosophila* frizzled and frizzled2 act in the wingless pathway as determined by dsRNA-medication genetic interference. *Cell* 95: 1017–1026.
- Jorgensen, R.A., et al., (1999) Do unintended antisense transcripts contribute to sense co-suppression in plants? *Trends in Genetics* 15: 11–12.
- Misquitta, L., and Paterson, B.M. (1999) Targeted disruption of gene function in *Drosophila* by RNA interference (RNA-i): A role for nautilus in embryonic somatic muscle formation. *Proc. Natl. Acad. Sci.* 96: 1451–1456.
- Sharp, P.A. (1999) RNAi and double-stranded RNA. *Gene and Development* 13: 139–141.
- Seydoux, G., et al. (1996) Repression of gene expression in the embryonic germ lineage of *C. elegans*. *Nature* 382: 713–716.
- Stam, M., et al. (1997) The silence of genes in transgenic plants. *Annals of Botany* 79:3–12.
- Nellen, W., and Lichtenstein, C. (1993) What makes an mRNA anti-sense-itive? *Trends in Biochemical Sciences* 18: 419–423.
- Proud, C.G. (1995) PKR: A new name and new roles. *Trends in Biochemical Sciences* 20:241–246.
- Jacobs, B.L., and Langland, J.O. (1996) When two strands are better than one: The mediators and modulators of the cellular responses to double-stranded RNA. *Virology* 219: 339–349.
- Fire, A., et al., (1998) Potent and specific genetic interference by double-stranded RNA in *Caenorhabditis elegans*. *Nature* 391: 806–811.
- Fire, A., (1998) “RNAi info from the Fire Lab” (Web Document with protocols to accompany the Fire et al., *Nature* paper). Posted on our public-access web site from Feb. 1, 1998.
- Fire, A., and Fleenor, J. (1998) On the generality of RNA-mediated interference. *Worm Breeder’s Gazette* 15(3): 8 (Jun. 1, 1998).
- Li et al., “Double-stranded RNA injection produces null phenotypes in zebrafish” *Developmental Biology*, Jan. 15, 2000, 217:394–405.
- Wianny et al., “Specific interference with gene function by double-stranded RNA in early mouse development” *Nature Cell Biology*, Feb. 2000, 2:70–75.
- Catalanotto et al., “Gene silencing in worms and fungi” *Nature*, Mar. 16, 2000, 404:245.
- Hammond et al., “An RNA-directed nuclease mediates post-transcriptional gene silencing in *Drosophila* cells” *Nature*, Mar. 16, 2000, 404:293–296.
- Ketting and Plasterk, “A genetic link between co-suppression and RNA interference in *C. elegans*” *Nature*, Mar. 16, 2000, 404:296–298.
- Grishok et al., “Genetic Requirements for Inheritance of RNAi in *C. elegans*”, *Science*, vol. 287, Mar. 31, 2000, pp. 2494–2497.
- Sharp et al., “RNA Interference”, *Science*, vol. 287, Mar. 31, 2000, pp. 2431 and 2433.
- Baker et al., “RNAi of the receptor tyrosine phosphatase HmLAR2 in a single cell of an intact leech embryo leads to growth-cone collapse,” *Current Biology* (2000) vol. 10, pp. 1071–1074.
- Bass, “Double-stranded RNA as a template for gene silencing,” *Cell* (2000 vol. 101, pp. 235–238.
- Bastin et al., “Flagellum ontogeny in trypanosomes studied via an inherited and regulated RNA interference system,” *J Cell Science* (2000) vol. 113, pp. 3321–3328.
- Baulcombe, “Unwinding RNA silencing,” *Science* (2000) vol. 290, pp. 1108–1109.
- Bhat et al., “Discs Lost, a novel multi-PDZ domain protein, establishes and maintains epithelial polarity,” *Cell* (1999), vol. 96, pp. 833–845.
- Bosher et al., “RNA interference: genetic wand and genetic watchdog,” *Nature Cell Biology* (2000) vol. 2, pp. E31–E36.
- Caplen et al., “dsRNA-mediated gene silencing in cultured *Drosophila* cells: a tissue culture model for the analysis of RNA interference,” *Gene* (2000), vol. 252, pp. 95–105.

- Chuang et al., "Specific and heritable genetic interference by double-stranded RNA in *Arabidopsis thaliana*," PNAS (2000) vol. 97, pp. 4985-4990.
- Colussi et al., "Debel, a proapoptotic Bcl-2 homologue, is a component of the *Drosophila melanogaster* cell death machinery," J Cell Biology (2000) vol. 148, pp. 703-714.
- Denef et al., "Hedgehog induces opposite changes in turnover and subcellular localization of Patched and Smoothed," Cell (2000) vol. 102, pp. 521-531.
- Domeier et al., "A link between RNA interference and nonsense-mediated decay in *Caenorhabditis elegans*," Science (2000) vol. 289, pp. 1928-1930.
- Fagard et al., "AGO1, ODE-2, and RDE-1 are related proteins required for post-transcriptional gene silencing in plants, quelling in fungi, and RNA interference in animals," PNAS (2000) vol. 97, pp. 11650-11654.
- Fortier et al., "Temperature-dependent gene silencing by an expressed inverted repeat in *Drosophila*," Genesis (2000) vol. 26, pp. 240-244.
- Fraser et al., "Functional genomic analysis of *C. elegans* chromosome I by systematic RNA interference," Nature (2000) vol. 408, pp. 325-330.
- Hill et al., "dpy-18 Encodes an  $\alpha$ -subunit of prolyl-4-hydroxylase in *Caenorhabditis elegans*," Genteics (2000) vol. 155, pp. 1139-1148.
- Hsieh et al., "The Ring finger/B-Box Factor TAM-1 and a retinoblastoma-like protein LIN-35 modulate context-dependent gene silencing in *Caenorhabditis elegans*," Genes & Development (1999) vol. 13, pp. 2958-2970.
- Huang et al., "The proneural gene amos promotes multiple dendritic neuron formation in the *Drosophila* peripheral nervous system," Neuron (2000) vol. 25, pp. 57-67.
- Hughes et al., "RNAi analysis of Deformed, proboscipedia and Sex combs reduced in the milkweed bug *Oncopeltus fasciatus*: novel roles for Hox genes in the Hemipteran head," Development (2000) vol. 127, pp. 3683-3694.
- Hunter, "Gene silencing; Shrinking the black box of RNAi," Current Biology (2000) vol. 10, pp. R137-R140.
- Kennerdell et al., "Heritable gene silencing in *Drosophila* using double-stranded RNA," Nature Biotechnology (2000) vol. 17, pp. 896-898.
- Kim et al., "Positioning of longitudinal nerves in *C. elegans* by nidogen," Science (2000) vol. 288, pp. 150-154.
- Kostich et al., "Identification and molecular-genetic characterization of a LAMP/CD68-like protein from *Caenorhabditis elegans*," J Cell Science (2000) vol. 113, pp. 2595-2606.
- Lam et al., "Inducible expression of double-stranded RNA directs specific genetic interference in *Drosophila*," Current Biology (2000) vol. 10, pp. 957-963.
- Lewis et al., "Distinct roles of the homeotic genes Ubx and abd-A in beetle embryonic abdominal appendage development," PNAS (2000) vol. 97, pp. 4504-4509.
- Liu et al., "Overlapping roles of Two Hox genes and the exd ortholog ceh-20 in diversification of the *C. elegans* postembryonic mesoderm," Development (2000) vol. 127, pp. 5179-5190.
- Liu et al., "Essential roles for *Caenorhabditis elegans* lamin gene in nuclear organization, cell cycle progression, and spatial organization of nuclear pore complexes," Molecular Biology Cell (2000) vol. 11, pp. 3937-3947.
- Lohmann et al., "Silencing of developmental genes in Hydra," Developmental Biology (1999) vol. 214, pp. 211-214.
- Maine, "A conserved mechanism for post-transcriptional gene silencing?" Genome Biology (2000) vol. 1, pp. 1018.1-1018.4.
- Mette et al., "Transcriptional silencing and promoter methylation triggered by double-stranded RNA," The EMBO Journal (2000) vol. 19, pp. 5194-5201.
- Marx, "Interfering with gene expression," Science (2000) vol. 288, pp. 1370-1372.
- Melendez et al., "*Caenorhabditis elegans* lin-13, a member of the LIN-35 Rd class of genes involved in vulval development, encodes a protein with zinc fingers and an LXCXE motif," Genetics (2000) vol. 155, pp. 1127-1137.
- Nakano et al., "RNA interference for the organizer-specific gene Xlim-1 in *Xenopus* embryos," Biochemical Biophysical Research Communications (2000) vol. 274, pp. 434-439.
- Oates et al., "Too much interference: Injection of double-stranded RNA has nonspecific effects in the zebrafish embryo," Developmental Biology (2000) vol. 224, pp. 20-28.
- Oelgeschläger et al., "The evolutionarily conserved BMP-binding protein Twisted gastrulation promotes BMP signalling," Nature (2000) vol. 405, pp. 757-763.
- Parrish et al., "Functional anatomy of a dsRNA trigger: Differential requirement for the two trigger strands in RNA interference," Molecular Cell (2000) vol. 6, pp. 1077-1087.
- Pichler et al., "OOC-3, a novel putative transmembrane protein required for establishment of cortical domains and spindle orientation in the P<sub>1</sub> blastomere of *C. elegans* embryos," Development (2000) vol. 127, pp. 2063-2073.
- Pineda et al., "Searching for the prototypic eye genetic network: *Sine oculis* is essential for eye regeneration in planarians," PNAS (2000) vol. 97, pp. 4525-4529.
- Sawa et al., "Components of the SWI/SNF complex are required for asymmetric cell division in *C. elegans*," Molecular Cell (2000) vol. 6, pp. 617-624.
- Shi et al., "Genetic interference in *Trypanosoma brucei* by heritable and inducible double-stranded RNA," RNA (2000) vol. 6, pp. 1069-1076.
- Shippy et al., "Analysis of maxillopedia expression pattern and larval cuticular phenotype in wild-type and mutant *Tribolium*," Genetics (2000) vol. 155, pp. 721-731.
- Stauber et al., "Function of bicoid and hunchback homologs in the basal cyclorrhaphan fly *Megaselia* (Phoridae)," PNAS (2000) vol. 97, pp. 10844-10849.
- Svoboda et al., "Selective reduction of dormant maternal mRNAs in mouse oocytes by RNA interference," Development (2000) vol. 127, pp. 4147-4156.
- Tavernarakis et al., "Heritable and inducible genetic interference by double-stranded RNA encoded by transgenes," Nature Genetics (2000) vol. 24, pp. 180-183.
- Ui-Tei et al., "Sensitive assay of RNA interference in *Drosophila* and Chinese hamster cultured cells using firefly luciferase gene as target," FEBS Letters (2000) vol. 479, pp. 79-82.
- Wang et al., "Inhibition of *Trypanosoma brucei* gene expression by RNA interference using an integratable vector with opposing T7 promoters," J Biological Chemistry (2000) electronically published as Manuscript M008405200, pp. 1-30 and figures 1-6.
- Willert et al., "A *Drosophila* Axin homolog, Daxin, inhibits Wnt signaling," Development (1999) vol. 126, pp. 4165-4173.

- Wu-Scharf et al., "Transgene and transposon silencing in *Chlamydomonas reinhardtii* by a DEAH-box RNA helicase," *Science* (2000) vol. 290, pp. 1159-1162.
- Yang et al., "Evidence that processed small dsRNAs may mediate sequence-specific mRNA degradation during RNAi in *Drosophila* embryos," *Current Biology* (2000) vol. 10, pp. 1191-1200.
- Zamore et al., "RNAi: Double-stranded RNA directs the ATP-dependent cleavage of mRNA at 21 to 23 nucleotide intervals," *Cell* (2000) vol. 101, pp. 25-33.
- Parrish et al. "Functional anatomy of a dsRNA trigger: Differential requirements for the two trigger strands in RNA interference" *Mol. Cell* (2000) 6: 1077-1087.
- Elbashir et al. "RNA interference mediated by 21- and 22-nucleotide RNA" *Genes Dev.* (2001) 15: 188-200.
- Elbashir et al. "Duplexes of 21-nucleotide RNAs mediate RNA interference in cultured mammalian cells" *Nature* (2001) 411: 494-498.
- Bass "The short answer" *Nature* (2001) 411: 428-429.
- Davenport "A faster way to shut down genes" *Science* (2001) 292:1469-1471.
- Hutvagner et al. "A cellular function for the RNA-interference enzyme Dicer in the maturation of the let-7 small temporal RNA" *Science* (2001) 294: 834-838.
- Grishok et al. "Genes and mechanisms related to RNA interference regulate expression of the small temporal RNAs that control *C. elegans* developmental timing" *Cell* (2001) 106: 23-34.
- Caplen et al. "Specific inhibition of gene expression by small double-stranded RNAs in invertebrate and vertebrate systems" *Proc Natl Acad Sci USA* (2001) early edition pnas.171251798 pp. 1-6.
- Ratcliff F et al: "A similarity between viral defense and gene silencing in plants", *Science*, vol. 276, No. 93, Jun. 6, 1997, pp. 1558-1560, XP002095874, see the whole document.
- Fire, A. et al. "Production of antisense RNA leads to effective and specific inhibition of gene expression in *C. elegans* muscle", *Development* (Cambridge, UK) (1991), 113(2), 503-14 XP002103600 cited in the application, see page 508, right-hand column, paragraph 2, see page 509, right-hand column—p. 511, right-hand column, see page 512, 'Discussion' and figure 7.
- Matzek M A et al.: "How and Why Do Plants Inactivate Homologous (Trans) Genes?", *Plant Physiology*, vol. 107, No. 3, 1 Mar. 1995, pp. 679-685, XP002021174, see p. 680, left-hand column, paragraph 3—right-hand column, paragraph 1, see page 682.
- Fire A et al: "Potent and specific genetic interference by double-stranded RNA in *Caenorhabditis elegans*", *Nature*, (Feb. 19, 1998 ) 391 (6669) 806-11., XP002095876, cited in the application, see the whole document.
- Montgomery M K et al: "Double-stranded RNA as a mediator in sequence-specific genetic silencing and co-specific genetic silencing and co-suppression", *Trends in Genetics*, (Jul. 1998) 14 (7) 255.8., XP004124680, cited in the application, see the whole document.
- Timmons L et al: "Specific interference by ingested dsRNA", *Nature*, (Oct. 29, 1998) 395 (6705) 854., XP002103601, cited in the application, see the whole document.
- Samuel E. Driver, Gregory S. Robinson, Jean Flanagan, Wei Shen, Lois E.H. Smith, David W. Thomas, and Peter C. Roberts, "Oligonucleotide-based inhibition of embryonic gene expression," *Nature Biotechnology*, vol. 17, Dec. 1999, pp. 1184-1187.
- Alejandro Sanchez Alvarado and Phillip A. Newmark, "Double-stranded RNA specifically disrupts gene expression during planarian regeneration," *Proc. Natl. Acad. Sci. USA*, vol. 96, Apr. 1999, *Developmental Biology*, pp. 5049-5054.
- James D. Thompson, "Shortcuts from gene sequence to function," *Nature Biotechnology*, vol. 17, Dec. 1999, pp. 1158-1159.
- Baum et al., "Inhibition of protein synthesis in reticulocyte lysates by a double-stranded RNA component in HeLa mRNA" *Biochem Biophys Res Comm*, Jul. 18, 1983, 114:41-49.
- Pratt et al., "Regulation of in vitro translation by double-stranded RNA in mammalian cell mRNA preparations" *Nucl Acids Res*, Feb. 25, 1988, 16:3497-3510.
- Klaff et al., "RNA structure and the regulation of gene expression" *Plant Mol Biol*, 1996, 32:89-106.
- Dolnick, "Naturally occurring antisense RNA" *Pharmacol Ther*, 1997, 75:179-184.
- Wagner et al., "Double-stranded RNA poses puzzle" *Nature*, Feb. 19, 1998, 391:744-745.
- Harbinder et al., "Genetically targeted cell disruption in *Caenorhabditis elegans*" *Proc Natl Acad Sci USA*, Nov. 1997, 94:13128-131133.
- Harcourt et al., "Ebola virus inhibits induction of genes by double-stranded RNA in endothelial cells" *Virology*, 1998, 252:179-188.
- Kumar and Carmichael, "Antisense RNA: Function and fate of duplex RNA in cells of higher eukaryotes" *Microbiol Mol Biol Rev*, Dec. 1988, 62:1415-1434.
- Suzuki et al., "Activation of target-tissue immune-recognition molecules by double-stranded polynucleotides" *Proc Natl Acad Sci USA*, Mar. 1999, 96:2285-2290.
- Hunter, "A touch of elegance with RNAi" *Curr Biol*, Jun. 17, 1999, 9:R440-R442.
- Tuschi et al., "Targeted mRNA degradation by double-stranded RNA in vitro" *Genes Dev*, Dec. 15, 1999, 13:3191-3197.
- Fire, "RNA-triggered gene silencing" *Trends Genet*, Sep. 1999, 15:358-363.
- Tabara et al., "The rde-1 Gene, RNA interference, and transposon silencing in *C. elegans*" *Cell*, Oct. 15, 1999, 99:123-132.
- Ketting et al., "Mut-7 of *C. elegans*, required for transposon silencing and RNA interference, is a homolog of Werner syndrome helicase and RNaseD" *Cell*, Oct. 15, 1999, 99:133-141.
- Bosher et al., "RNA interference can target pre-mRNA: Consequences for gene expression in a *Caenorhabditis elegans* operon" *Genetics*, Nov. 1999, 153:1245-1256.
- Thompson, "Shortcuts from gene Sequence to function" *Nature Biotechnology*, Dec. 1999, 17:1158-1159.
- Driver et al., "Oligonucleotide-based inhibition of embryonic gene expression" *Nature Biotechnology*, Dec. 1999, 17:1184-1187.
- Wargelius et al., "Double-stranded RNA induces specific developmental defects in zebrafish embryos" *Biochem Biophys Res Comm*, 1999, 263:156-161.

\* cited by examiner

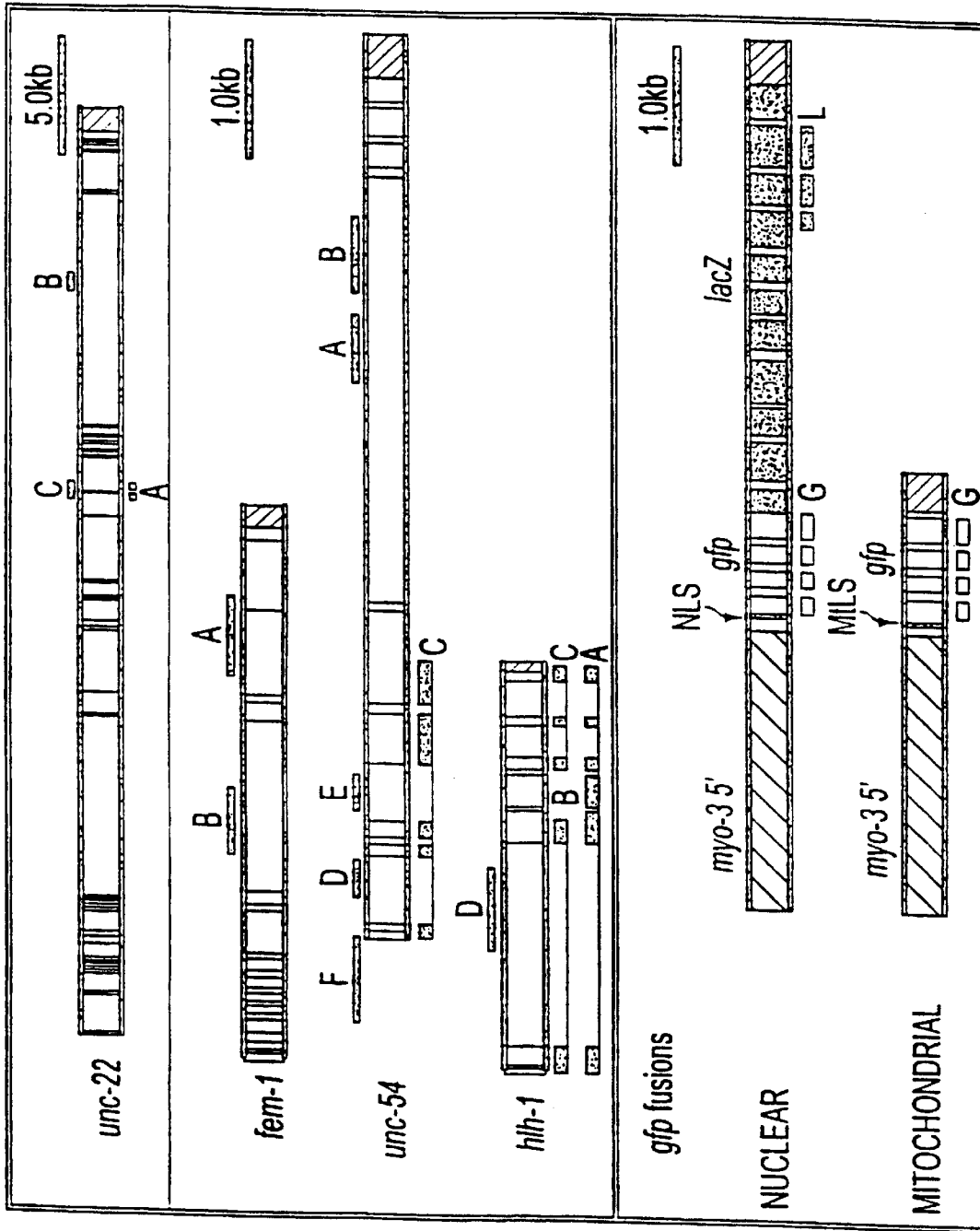


FIG. 1

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