



(86) Date de dépôt PCT/PCT Filing Date: 2002/05/14
(87) Date publication PCT/PCT Publication Date: 2002/11/21
(85) Entrée phase nationale/National Entry: 2003/11/13
(86) N° demande PCT/PCT Application No.: US 2002/015198
(87) N° publication PCT/PCT Publication No.: 2002/092840
(30) Priorité/Priority: 2001/05/14 (60/290,927) US

(51) Cl.Int.⁷/Int.Cl.⁷ C12N 15/55, A61K 38/46, A61P 35/00,
C12Q 1/02, C12N 9/22, C12N 15/11, G01N 33/53

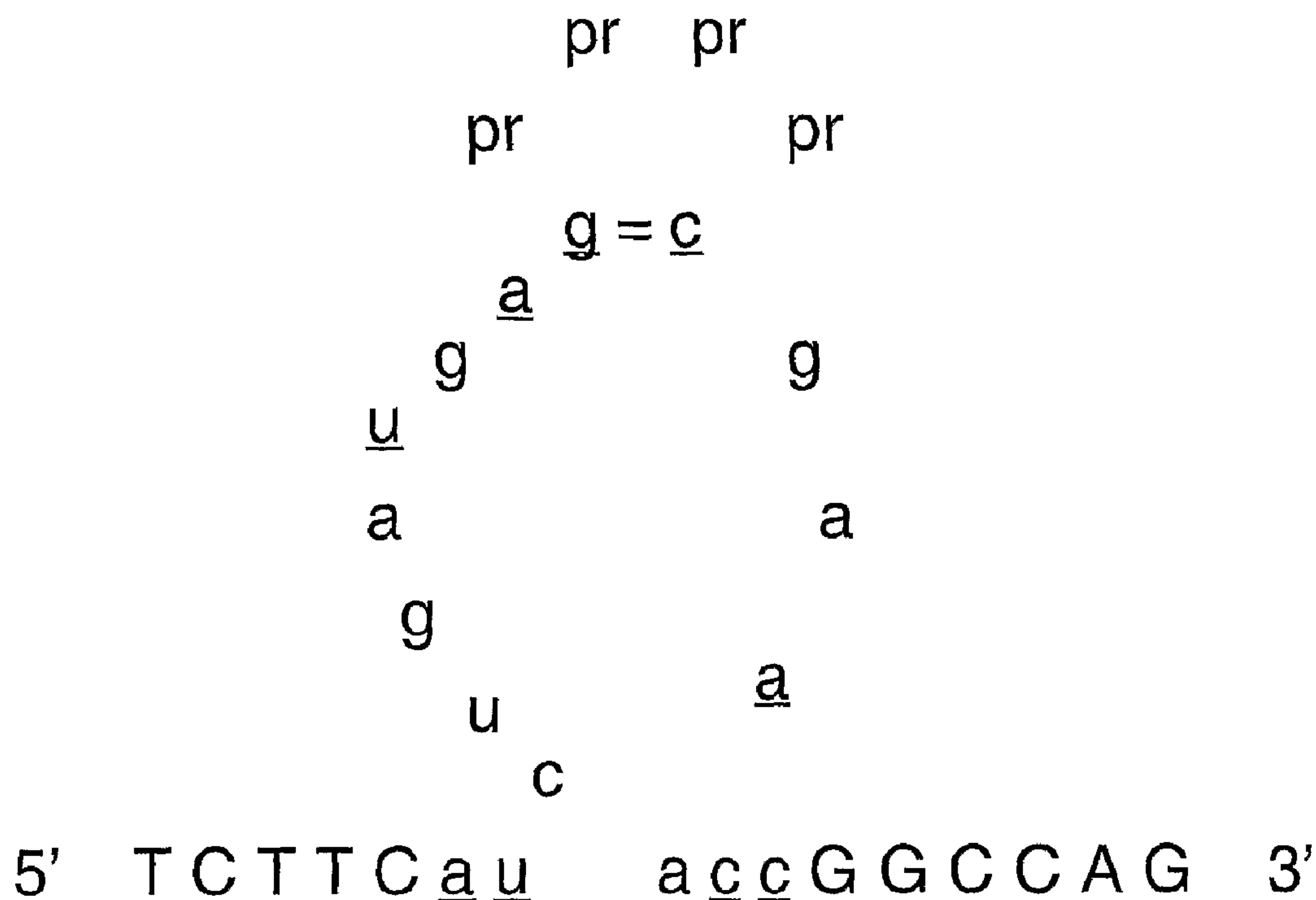
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(54) Titre : AGENTS REGULATEURS DE L'APOPTOSE

(54) Title: AGENTS THAT REGULATE APOPTOSIS



(57) Abrégé/Abstract:

The present invention provides genes, nucleic acid sequences, proteins and amino acid sequences that are involved in the inhibition of apoptosis induction in cells. The invention also provides the RNA correlates of these genes and nucleic acid sequences. Further provided are isolated nucleic acid molecules that interact with the genes, nucleic acid sequences and RNA correlates disclosed herein, such that their inhibitory effect on apoptosis induction is lessened and, therefore, apoptosis induction is facilitated.



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
21 November 2002 (21.11.2002)

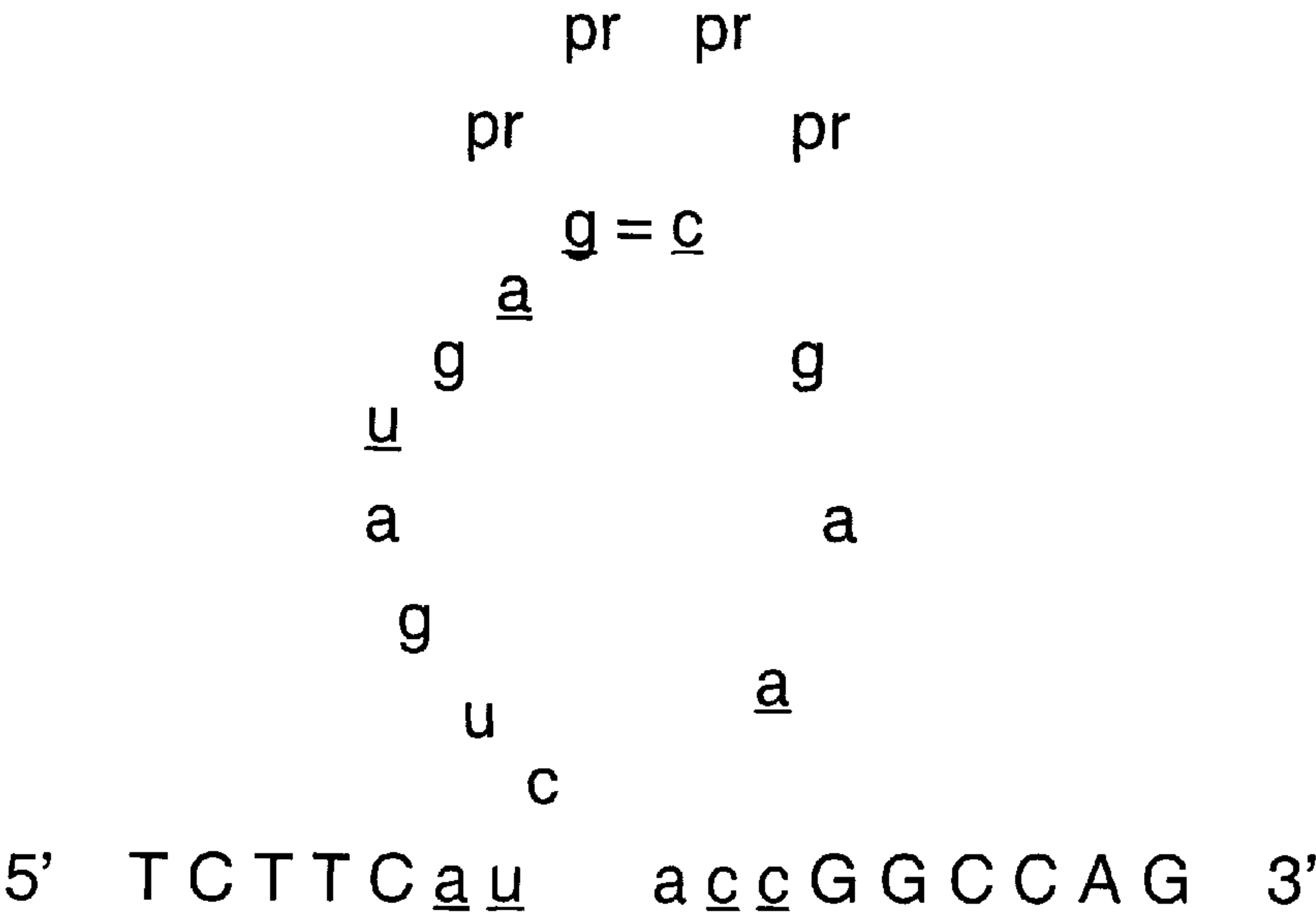
PCT

(10) International Publication Number
WO 02/092840 A2

- (51) International Patent Classification⁷: C12Q
- (21) International Application Number: PCT/US02/15198
- (22) International Filing Date: 14 May 2002 (14.05.2002)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/290,927 14 May 2001 (14.05.2001) US
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- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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(54) Title: AGENTS THAT REGULATE APOPTOSIS



(57) Abstract: The present invention provides genes, nucleic acid sequences, proteins and amino acid sequences that are involved in the inhibition of apoptosis induction in cells. The invention also provides the RNA correlates of these genes and nucleic acid sequences. Further provided are isolated nucleic acid molecules that interact with the genes, nucleic acid sequences and RNA correlates disclosed herein, such that their inhibitory effect on apoptosis induction is lessened and, therefore, apoptosis induction is facilitated.

WO 02/092840 A2

WO 02/092840 A2



Published:

— *without international search report and to be republished
upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

AGENTS THAT REGULATE APOPTOSIS

FIELD OF THE INVENTION

The invention relates generally to the identification of agents involved in disease processes and more particularly to the identification of genes, nucleic acid
5 sequences, proteins and amino acid sequences involved in the inhibition of apoptosis induction. The invention also relates to the identification of nucleic acids encoding ribozymes, the ribozymes themselves and their use for facilitating the induction of apoptosis.

BACKGROUND OF THE INVENTION

10 Apoptosis or programmed cell death is an active process of gene-directed cellular self-destruction that contrasts fundamentally with degenerative death or necrosis. Apoptotic cell death is characterized by cellular shrinkage, chromatin condensation, cytoplasmic blebbing, increased membrane permeability and interchromosomal DNA cleavage.

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The process of programmed cell death through apoptosis is connected with a variety of normal and pathogenic biological events and can be induced by a number of unrelated stimuli. Many biological processes, including embryogenesis, immune system responses, elimination of virus-infected cells, and the maintenance of tissue homeostasis
20 involve apoptosis. Changes in the biological regulation of apoptosis also occur during aging and are responsible for many of the conditions and diseases related to aging.

Because of the role apoptosis plays in normal physiology, the failure of apoptosis to occur in such processes can contribute to disease. For example, substantial
25 evidence has accumulated that inhibition of apoptotic processes is involved in the formation or growth of cancer. As a result, the elimination of cancer cells through

induction of apoptotic cell death is now considered a promising approach in cancer therapy. A variety of chemotherapeutic compounds as well as ionizing radiation that have been used successfully in cancer treatments have been demonstrated to induce apoptosis in tumor cells, for example by activating well known apoptosis induction genes
5 such as wild-type p53.

However, the process of apoptosis induction in cancer and in other disease states is complex and much more needs to be done to identify genes and gene products involved in regulating apoptosis. In this regard, the discovery of new agents that affect
10 the activity of genes or gene products that inhibit apoptosis will have therapeutic utility in a wide variety of conditions. The present invention addresses these needs and provides related advantages as well.

SUMMARY OF THE INVENTION

15 The present invention provides genes, nucleic acid sequences, proteins and amino acid sequences that are involved in the inhibition of apoptosis induction in cells. The invention also provides the RNA correlates of these genes and nucleic acid sequences. Further provided are isolated nucleic acid molecules that interact with the genes, nucleic acid sequences and RNA correlates disclosed herein, such that their
20 inhibitory effect on apoptosis induction is lessened and, therefore, apoptosis induction is facilitated.

The isolated nucleic acid molecules of the invention include nucleotide sequences encoding ribozymes. The ribozymes of the invention have “substrate binding
25 sequences” that hybridize to and cleave complementary sequences of the mRNA encoded by the genes and gene sequences disclosed herein and, therefore, facilitate apoptosis. Included within the scope of the invention are expression vectors encoding the ribozymes, cells containing the vectors and cells expressing the ribozymes. In addition,

as shown for instance in Example 6, a ribozyme of the present invention can be introduced directly into a cell, i.e., without the use of a vector.

5 The present invention further provides a method for facilitating the induction of apoptosis in cells, for example cells resistant to apoptosis induction such as cancer cells, by introducing a ribozyme of the invention into such cells. For example, the cells can be transduced with expression vectors encoding ribozymes of the invention and, optionally, an apoptosis inducing agent can be introduced in the cells.

10 The present invention further provides a method for identifying an agent that can facilitate induction of apoptosis in cells, for example those resistant to apoptosis induction. The method comprises contacting a protein or polypeptide encoded by the genes and gene sequences disclosed herein, or contacting these genes or gene sequences themselves, with the agent and measuring the level or activity of the protein or
15 polypeptide. A reduction in level would indicate that the agent can facilitate induction of apoptosis. Representative agents include antisense oligonucleotides, monoclonal and polyclonal antibodies, and small molecule drugs.

BRIEF DESCRIPTION OF THE DRAWINGS

20 Figure 1 shows the general structure and nucleotide sequence of a hairpin ribozyme (large case lettering) (SEQ ID NO: 1) and its interaction with a substrate RNA (small case lettering) (SEQ ID NO: 2).

25 Figure 2 shows the general structure and nucleotide sequence of a hammerhead ribozyme (large case lettering) (SEQ ID NO: 3) and its interaction with a substrate RNA (small case lettering) (SEQ ID NO: 4).

Figure 3 shows the structure of the RAP6 chimeric hammerhead ribozyme (SEQ ID NO: 5). In the Figure, "pr" indicates propylenediol; the remaining upper case letters (e.g., T, C, G and A) indicate DNA bases; the lower case letters indicate RNA bases; and the underlined lower case letters indicate RNA bases with $-OCH_3$ attached at the 2-position of that base's sugar moiety.

Figure 4 shows the structure of the TV2-2 (Est2-2) chimeric hammerhead ribozyme (SEQ ID NO: 6). In the Figure, "pr" indicates propylenediol; the remaining upper case letters (e.g., T, C, G and A) indicate DNA bases; the lower case letters indicate RNA bases; and the underlined lower case letters indicate RNA bases with $-OCH_3$ attached at the 2-position of that base's sugar moiety.

Figure 5 shows the pLPR retroviral vector used to clone the ribozyme gene vector library.

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Figure 6 shows Taqman analysis of mRNA target knockdown of the EST2 gene using the RAP2 and TV2-1 (Est2-1) ribozymes.

Figure 7 shows a radiograph of Northern blot analysis of colon tumor cells and normal colon tissue.

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Figure 8 shows the level of apoptosis in cancer cells (anaplastic transitional cell carcinoma urinary bladder cells) when transfected: 1) with the TV2-2 (Est2-2) chimeric hammerhead ribozyme; 2) with the TV2-2 (Est2-2) chimeric hammerhead ribozyme and Fas; 3) with the SR6 (RAP6) chimeric hammerhead ribozyme; 4) with the SR6 (RAP6) chimeric hammerhead ribozyme and Fas; 5) with the TV2-2 (Est2-2) chimeric hammerhead ribozyme and the SR6 (RAP6) chimeric hammerhead ribozyme; and 6) with the TV2-2 (Est2-2) chimeric hammerhead ribozyme and the SR6 (RAP6) chimeric hammerhead ribozyme and Fas.

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DETAILED DESCRIPTION OF INVENTION

The present invention provides isolated nucleic acid molecules encoding ribozymes, each ribozyme having a "substrate binding sequence" that recognizes a target nucleic acid molecule involved in the inhibition of apoptosis induction. The ribozymes of the invention are catalytic RNA molecules that bind to the target nucleic acid molecules and cleave them, thereby impairing their ability to function as inhibitors of apoptosis induction. The ribozymes of the invention are identified and selected by methods described herein. They may be "hairpin" ribozymes, "hammerhead" ribozymes or any other type of ribozyme known in the art.

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Figure 1 illustrates the basic structure and nucleotide sequence (shaded, in uppercase letters) of a hairpin ribozyme (SEQ ID NO: 1) and its relationship to the complementary nucleotide sequence (lowercase letters; SEQ ID NO: 2) of a target substrate (N or n = any nucleotide). A hairpin ribozyme consists of a 50 to 54 nucleotide RNA molecule, with the non-substrate binding sequence beginning from the 5' end at nucleotide position 17. It folds into a 2-dimensional structure that resembles a hairpin, consisting of two helical domains (Helix 3 and 4) and 3 loops (Loop 2, 3 and 4) and two additional helices (Helix 1 and 2), which form between the ribozyme and the substrate. The length of Helix 2 is fixed at 4 base pairs and the length of Helix 1 typically varies from 6 to 10 base pairs. Recognition of the substrate nucleotides by the ribozyme occurs via Watson-Crick base pairing, with typical substrate recognition sites having the structure 5'-GUC-3' or 5'-GUA-3'. For maximal activity, the RNA target substrate can contain a GUC in a loop that is opposite Loop 1 with cleavage occurring immediately 5' of the G as indicated by an arrow. The catalytic, but not substrate binding, activity of a hairpin ribozyme can be disabled by mutating the 5'-AAA-3' in Loop 2 to 5'-CGU-3'.

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The general structure of a hammerhead ribozyme is shown in Figure 2 (SEQ ID NO: 3) along with its target RNA sequence (SEQ ID NO: 4). Hammerhead

ribozymes suitable for use within the present invention preferably recognize the sequence NUH, wherein N is any of G, U, C, or A and H is C, U, or A. It will be appreciated that the recognition sites of the hairpin ribozyme of the present invention (5'-GUC-3' or 5'-GUA-3') are a subset of the hammerhead recognition sites (5'-NUH-3'), such that all
5 hairpin recognition sites are by definition also hammerhead recognition sites, although the converse is not true.

Chimeric hammerhead ribozyme (i.e., RNA/DNA hybrids) are designed to recognize the appropriate NUH sequence for cleavage. Generally, most or all of the
10 binding arms and stem loop comprise DNA. By contrast, generally, the catalytic domain (shown in Figure 2 between the binding arms and stem loop) comprises RNA.

Modification of the base composition at the stem loop or catalytic domain regions can increase the catalytic activity of the ribozyme, as assayed by in vitro cleavage
15 See WO 00/32765. Modification at the 2-position of the sugar of the base, for example, substituting -OCH₃ at this position of an RNA base, can increase the stability of the ribozyme. Other stabilizing substitutions include -OC₁₋₆Alkyl, -F or other halogens, amino, azido, nitro and phenyl. See U.S. Pat. No. 5,298,612.

20 The term, "substrate binding sequence" of a ribozyme, as used herein, refers to that portion of the ribozyme which base pairs with a complementary sequence (referred to herein as a "ribozyme sequence tag" or "RST") of a target nucleic acid. For example, the 16 nucleotides at the 5' end of the sequence of Figure 1 (SEQ ID NO:) represent the general formula for a hairpin ribozyme substrate binding sequence. This
25 includes the two arms that form helixes with the target and any necessary nucleotides between these two arms that may be required for the ribozyme function (e.g., AAGA or AAGC). The general formula for the substrate binding sequence of a hammerhead ribozyme is shown in Figure 2 (SEQ ID NO: 3) with the substrate binding sequence

shown aligned with the complementary sequence (RST) of the target RNA (SEQ ID NO: 4).

Because of the basic similarity in the structure of all hairpin ribozymes, they can be modified to obtain a ribozyme having a specific substrate binding sequences of choice. For example, the substrate binding sequence of a "GUC ribozyme", which cleaves an RNA having the sequence 5'-NNNNN*GUCNNNNNNNNN (SEQ ID NO: 7) may be modified to that of a "GUA ribozyme," which cleaves an RNA having the sequence 5' - NNNNN*GUANNNNNNNN (SEQ ID NO: 8), by changing the base at position 9 from the 5' end of the substrate binding sequence of the ribozyme. In both of these sequences, N is any of G, U, C, or A; and the asterisk indicates the site where cleavage of the target RNA occurs.

A preferred "GUC hairpin ribozyme" has a substrate binding sequence with the general formula 5'-(N)₍₆₋₁₀₎AGAA(N)₄-3' (SEQ ID NO: 9), where N can be either G, T, C, or A. A preferred "GUA hairpin ribozyme" has a substrate binding sequence with the general formula 5'-(N)₍₆₋₁₀₎CGAA(N)₄-3' (SEQ ID NO: 10), where N can be either G, T, C, or A. In the case of the specific ribozyme substrate binding sequences disclosed herein based on these formulas, the sequences also include variations where no more than two nucleotides differ at any of positions 1-5 from the 5' end of the sequence. This means that one may change one or two bases within the first 5 nucleotides at the 5' end of a substrate binding sequence and still retain the functional activity of the ribozyme.

Similarly, once the substrate binding sequence of a specific hairpin ribozyme has been identified, it is relatively easy to engineer an equivalent substrate binding sequence for a hammerhead ribozyme. The general structure of the substrate binding sequence of a hammerhead includes six to nine bases at the 5' end of the ribozyme's binding arm and six to nine bases at the 3' end of the other binding arm. The

following approach, for example, may be used: 1) identify the ribozyme sequence tag (RST) of the RNA target of the specific hairpin ribozyme of interest; 2) specify the first six to nine nucleotides at the 5' end of the hammerhead as complementary to the first six to nine nucleotides at the 3' end of the RST; 3) specify the first 5 nucleotides at the 3' end of the hammerhead as complementary to nucleotides at the 5' end of the RST; and 4) specify nucleotides at positions 6 and 7 from the 3' end of the hammerhead as complementary to the RST, while base 8 from the 3' end is an A.

It should therefore be understood that a ribozyme of the present invention can comprise a) 3, 4, 5, 6, 7, 8 or 9 contiguous bases of any of the ribozyme substrate binding sequences disclosed herein as part of one binding arm of the ribozyme; and b) 3, 4, 5, 6, 7, 8 or 9 contiguous bases of any of the remaining contiguous bases of that ribozyme substrate binding sequence as part of the other binding arm of the ribozyme.

A hammerhead ribozyme can be designed by incorporating sequences of one of the substrate binding sequences disclosed herein, for example bases 2 to 8 and 13 to 16 of the RAP6 substrate binding sequence (SEQ ID NO: 19), or bases 2 to 8 and 13 to 16 of the Est2-2 substrate binding sequence (SEQ ID NO: 97). Alternatively, bases 2 to 8 and 13 to 16 of other substrate binding sequences, for example RAP2 (SEQ ID NO: 17), RAP4: (SEQ ID NO: 18), RAP10 (SEQ ID NO: 20), RAP594 (SEQ ID NO: 21), NHMCZF-4 (SEQ ID NO: 46), Est2-1 (SEQ ID NO: 96), FA5-VR1 (SEQ ID NO: 134) and FA5-VR5 (SEQ ID NO: 138). Indeed, bases 2 to 8 and 13 to 16 of any ribozyme substrate binding sequence disclosed herein can be similarly incorporated into a hammerhead ribozyme.

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A preferred chimeric hammerhead ribozyme is SEQ ID NO: 5, which was designed to incorporate base sequences of RAP6 (SEQ ID NO: 19) and to bind to the RAP6 complementary RST (SEQ ID NO: 24). Another preferred chimeric hammerhead ribozyme is SEQ ID NO: 6, which was designed to incorporate base sequences of Est2-2

(SEQ ID NO: 97) and to bind to the Est2-2 complementary RST (SEQ ID NO: 99). As disclosed below in Example 6, these two chimeric hammerhead ribozymes can be used alone or in combination to facilitate induction of apoptosis in cells, for example cancer cells. Preferably these cells are resistant to apoptosis. Preferably, these ribozymes are
 5 used in combination with an apoptosis inducing agent, for example Fas.

In these preferred ribozymes, the stem loop comprises 1, 3-propylene- diol linkers. Unreacted, one –OH of the diol is substituted by –O(DMT), where DMT is dimethoxytrityl; and the other –OH is substituted by –O-P(O-CN-Et)-N(isopropyl)₂.
 10 When incorporated into the ribozyme, each –OH is substituted by -O(PO₄).

As used herein, the term “unmodified base” means one of the bases adenine, guanine, cytosine, uracil or thymine attached to the 1-carbon of the sugar (deoxyribose or ribo-furanose), with a phosphate bound to the 5-carbon of the sugar.
 15 Bases are bound to each other via phosphodiester bonds between the 3-carbon of one base and the 5-carbon of the next base.

As used herein, the term “modified base” means any base whose chemical structure is modified as follows. Adenine can be modified to result in 6-dimethyl-amino-purine, 6-methyl-amino-purine, 2-amino-purine, 2,6-diamino-purine, 6-amino-8-bromo-purine or 6-amino-8-fluoro-purine. Cytosine can be modified to result in 5-bromo-cytosine, 5-fluoro-cytosine, N,N-dimethyl-cytosine, N-methyl-cytosine, 2-thio-cytosine or 2-pyridone. Guanine can be modified to result in 8-bromo-guanine, 8-fluoroguanine, 2-amino-purine, hypoxanthine (inosine), 7-deaza-guanine or 6-thio-guanine. Uracil can
 20 be modified to result in 3-methyl-uracil, 5,6-dihydro-uracil, 4-thio-uracil, thymine, 5-bromo-uracil, 5-iodo-uracil or 5-fluoro-uracil. Thymine can be modified to result in 3-methyl-thymine, 5,6-dihydro-thymine, 4-thio-thymine, uracil, 5-bromo-uracil, 5-iodo-uracil or 5-fluoro-uracil. Methods of making such modifications as well as other modifications, such as halogen, hydroxy, amine, alkyl, azido, nitro and phenyl
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substitutions are disclosed in U.S. Pat. No. 5,891,684; and U.S. Pat. No. 5,298,612. The present invention encompasses sequences where one or more bases are modified.

In addition, the sugar moiety of a base can be modified as disclosed above
5 regarding bases of a hammerhead ribozyme. The present invention encompasses sequences where one or more bases are so modified.

As used herein, the term "nucleic acid" or "nucleic acid molecule" refers to deoxyribonucleotides or ribonucleotides, oligomers and polymers thereof, in either
10 single- or double-stranded form. Unless specifically limited, the term encompasses nucleic acids containing known analogues of natural nucleotides that have similar binding properties as the reference nucleic acid. For example, as disclosed herein, such analogues include those with substitutions, such as methoxy, at the 2-position of the sugar moiety. Unless otherwise indicated by the context, the term is used
15 interchangeably with gene, cDNA and mRNA encoded by a gene.

As used herein, the phrase "a nucleotide sequence encoding" refers to a nucleic acid which contains sequence information, for example, for a ribozyme, mRNA, structural RNA, and the like, or for the primary amino acid sequence of a specific protein
20 or peptide. In reference to a ribozyme, unless otherwise indicated, the explicitly specified encoding nucleotide sequence also implicitly covers sequences that do not materially effect the specificity of the ribozyme for its target nucleic acid. In reference to a protein or peptide, unless otherwise indicated, the explicitly specified encoding nucleotide sequence also implicitly encompasses variations in the base sequence encoding the same
25 amino acid sequence (*e.g.*, degenerate codon substitutions). The invention also contemplates proteins or peptides with conservative amino acid substitutions. The identity of amino acids that may be conservatively substituted is well known to those of skill in the art. Degenerate codons of the native sequence or sequences may be chosen to conform with codon preference in a specific host cell.

As used herein, the term "RNA correlate" of a given DNA sequence means that sequence with "U" substituted for "T." For example, when every "n" of SEQ ID NO: 19 is "U" (uracil), it is the RNA correlate to SEQ ID NO: 19 when every "n" is "T" (thymine). The present invention encompasses all RNA correlates of every substrate binding sequence and complementary RST disclosed herein.

The term "sequence identity," when comparing two or more nucleic acid sequences or two or more amino acid sequences, means BLAST 2.0 computer alignment, using default parameters. BLAST 2.0 searching is described, for example by Tatiana et al., FEMS Microbiol. Lett., 174:247-250 (1999), and is available, for example, at <http://www.ncbi.nlm.nih.gov/gorf/bl2.html>.

The term "moderately stringent conditions," as used herein, means hybridization conditions that permit a nucleic acid molecule to bind to a second nucleic acid molecule that has substantial identity to the sequence of the first. Moderately stringent conditions are those equivalent to hybridization of filter-bound nucleic acid in 50% formamide, 5 X Denhart's solution, 5 X SSPE, 0.2% SDS at 42°C, followed by washing in 0.2 X SSPE, 0.2% SDS at 50°C. "Highly stringent conditions" are those equivalent to hybridization of filter-bound nucleic acid in 50% formamide, 5 X Denhart's solution, 5 X SSPE, 0.2% SDS at 42°C, followed by washing in 0.2 X SSPE, 0.2% SDS at 65°C. Other suitable moderately stringent and highly stringent conditions are known in the art and described, for example, in Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, New York (1992), and Ansubel et al., Current Protocols in Molecular Biology, John Wiley and Sons, Baltimore MD (1998).

In general, a nucleic acid molecule that hybridizes to a second one under moderately stringent conditions will have greater than about 60% identity, preferably greater than about 70% identity and, more preferably, greater than about 80% identity

over the length of the two sequences being compared. A nucleic acid molecule that hybridizes to a second one under highly stringent conditions will have greater than about 90% identity, preferably greater than about 92% identity and, more preferably, greater than about 95% identity over the length of the two sequences being compared.

5

As used herein, the term "isolated" when used in conjunction with a nucleic acid or protein, denotes that the nucleic acid or protein has been isolated with respect to the many other cellular components with which it is normally associated in the natural state. For example, an "isolated" gene of interest may be one that has been separated from open reading frames which flank the gene and encode a gene product other than that of the specific gene of interest. Such genes may be obtained by a number of methods including, for example, laboratory synthesis, restriction enzyme digestion or PCR. Likewise, an "isolated" protein may be substantially purified from a natural source or may be synthesized in the laboratory. A "substantially purified" nucleic acid or protein gives rise to essentially one band in an electrophoretic gel, and is at least 85% pure, more preferably at least 95% pure, and most preferably at least 99% pure.

As used herein, the term "expression vector" includes a recombinant expression cassette that has a nucleotide sequence that can be transcribed into RNA in a cell. The cell can further translate transcribed mRNA into protein. An expression vector can be a plasmid, virus, or nucleic acid fragment. Typically, the recombinant expression cassette portion of an expression vector includes the encoding nucleotide sequence to be transcribed (e.g. a ribozyme), operably linked to a promoter, or other regulatory sequence by a functional linkage in *cis*. In accordance with the present invention, an expression vector comprising a nucleotide sequence encoding ribozymes of the invention can be used to transduce cells suitable as hosts for the vector. Both procaryotic cells including bacterial cells such as *E. coli* and eukaryotic cells including mammalian cells may be used for this purpose.

As used herein, the term "promoter" includes nucleic acid sequences near the start site of transcription (such as a polymerase binding site) and, optionally, distal enhancer or repressor elements (which may be located several thousand base pairs from the start site of transcription) that direct transcription of the nucleotide sequence in a cell.

5 The term includes both a "constitutive" promoter such as a pol III promoter, which is active under most environmental conditions and stages of development or cell differentiation, and an "inducible" promoter, which initiates transcription in response to an extracellular stimulus, such as a particular temperature shift or exposure to a specific chemical. Promoters and other regulatory elements (*e.g.*, an origin of replication), and/or
10 chromosome integration elements such as retroviral long terminal repeats ("LTRs"), or adeno associated viral (AAV) inverted terminal repeats ("ITRs"), may be incorporated into an expression vector encoding ribozymes of the present invention as described in WO 00/05415 to Barber *et al.*

15 As used herein, the term "expresses" denotes that a given nucleic acid comprising an open reading frame is transcribed to produce an RNA molecule. It also denotes that a given nucleic acid is transcribed and translated to produce a polypeptide. Although the term may be used to refer to the transcription of a ribozyme, a ribozyme typically is not translated into a protein since it functions as an active (catalytic) nucleic
20 acid.

As used herein, the term "gene product" refers either to the RNA produced by transcription of a given nucleic acid or to the polypeptide produced by translation of a given nucleic acid.

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As used herein, the term "transduce" denotes the introduction of an exogenous nucleic acid molecule (*e.g.*, by means of an expression vector) inside the membrane of a cell. Exogenous DNA may or may not be integrated (covalently linked) into chromosomal DNA making up the genome of the cell. The exogenous DNA may be

maintained on an episomal element, such as a plasmid. In eukaryotic cells, a stably transduced cell is generally one in which the exogenous DNA has become integrated into the chromosome so that it is inherited by daughter cells through chromosome replication, or one which includes stably maintained extrachromosomal plasmids. This stability is demonstrated by the ability of the eukaryotic cell to establish cell lines or clones comprised of a population of daughter cells containing the exogenous DNA.

The term “transfection,” as used herein, means the genetic modification of a cell by uptake of an exogenous nucleic acid molecule (*e.g.*, by means of an expression vector).

As used herein, the term “ribozyme gene vector library” denotes a collection of ribozyme-encoding genes, typically within expression cassettes, in a collection of viral or other vectors. The vectors may be naked or contained within a capsid. Propagation of the ribozyme gene vector library can be performed as described in WO 00/05415 to Barber *et al.* The ribozyme-encoding genes of a ribozyme gene vector library, after transduction and transcription in appropriate cells, produce a collection of ribozymes.

In accordance with a preferred embodiment of the present invention, a random retroviral ribozyme gene vector library was propagated, as described in Example 1 below. The retroviral ribozyme gene vector library was then used to transduce DLD-1 colon carcinoma cells, as described in Example 2 below. DLD-1 colon carcinoma cells were chosen because they were found to be resistant to apoptosis (as indicated by antibody triggering of Fas (CD95), which facilitates induction of apoptosis). The cells were then subjected to apoptosis induction, and apoptotic cells were identified and separated. Genomic DNA was isolated from the apoptotic cells, and the ribozyme genes were rescued.

As described in Example 2, three rounds of successive vector transduction, apoptosis induction, cell selection and ribozyme gene rescue were performed. After the third round of selection, the inventors found that approximately 5-6% of the cells that had been transduced with the ribozyme gene vector library had entered apoptosis as compared
5 to 1-2% of the control cells.

Upon analysis of the nucleotide sequences of the ribozyme genes, the inventors observed that five ribozyme substrate binding sequences were predominant (see Example 2, Tables 1-5). The validity of these five ribozyme substrate binding sequences
10 for facilitating apoptosis induction was then confirmed, as described in Example 2 below.

In accordance with a preferred embodiment of the present invention, genes involved in the inhibition of apoptosis induction were identified, as more fully described in Example 3 below. Since ribozymes recognize their cognate targets by
15 sequence complementarity, the substrate binding sequence of the ribozymes of the present invention (see Tables 1-5) were used to identify the ribozyme sequence tags (RSTs) of the RNA that were cleaved by the ribozymes of the present invention and which were involved in the inhibition of apoptosis induction. The identified RSTs of the cognate targets of the ribozymes of the present invention are also set forth in Tables 1-5
20 below.

The present invention provides isolated molecules comprising any of the complementary RSTs listed in Tables 1 to 5 below; the complementary RST to NHMCZF-4, Est2-1, Est2-2, FA5-VR1 or FA5-VR5; or the complementary RSTs listed in Tables 7
25 and 9 below. In addition, any of these molecules can be 150 bases or shorter, 125 bases or shorter, 100 bases or shorter, 90 bases or shorter, 80 bases or shorter, 70 bases or shorter, 60 bases or shorter, 50 bases or shorter, 40 bases or shorter, 30 bases or shorter, 25 bases or shorter, or 16 bases in length. These molecules can inhibit induction of apoptosis or, alternatively, be used to identify agents that facilitate induction of apoptosis.

Once the RSTs of the cognate targets of the ribozymes of the present invention were identified, the inventors conducted a search of the various public gene databases (such as the nr (nonredundant) database, the EST (Expressed Sequence Tag)-
5 Human database, the EST-Mouse database, the dbEST database, and the like) using the "BLAST" program (Basic Local Alignment Search Tool; <http://www.ncbi.nlm.nih.gov/BLAST/>), to identify genes and gene fragments containing one or more of the RST sequences (Tables 1-5) identified in accordance with the present invention. As more fully described in Example 3 below, this search disclosed several
10 complete matches with gene sequences in the public databases.

In accordance with the present invention, the involvement in apoptosis inhibition of the gene sequences that matched the identified RSTs was then validated (see Example 3 below). Based upon the known sequences of the identified genes,
15 "validation" ribozymes were constructed having substrate binding sequences complementary to RST's of the identified genes, and these were engineered for expression in retroviral vectors in accordance with the present invention. The validation ribozymes were then expressed in cells and analyzed for their ability to facilitate apoptosis induction in accordance with the present invention. The results are set forth in
20 Example 3.

The present invention provides additional nucleic acid sequences that contain EST2 (SEQ ID NO: 31), which is involved in inhibiting apoptosis induction (see Example 3). Specifically included in the present invention and described in Example 5,
25 are sequences comprising or consisting of a "contig," or contiguous sequence, of about 1.7 kb (SEQ ID NO: 146), about 2 kb (SEQ ID NO: 148), about 2.3 kb (SEQ ID NO: 150), about 2.6 kb (SEQ ID NO: 152), about 3.4 kb (SEQ ID NO: 155), about 4.1 kb (SEQ ID NO: 157) and about 5.5 kb (SEQ ID NO: 166). Also provided are the RNA correlate of each of these sequences as well as compounds having 90%, 91%, 92%, 93%,

94%, 95%, 96%, 97%, 98% and, most preferably, 99% sequence identity with any of these sequences. Also provided are compounds that hybridize under moderately or, more preferably, stringent conditions with any of these sequences.

5 The present invention also provides a method of facilitating the induction of apoptosis in a cell resistant to induction of apoptosis. This method comprises introducing a ribozyme of the invention into a cell, for example one resistant to apoptosis. This method can comprise transducing the apoptosis induction resistant cell with an expression vector encoding a ribozyme with a substrate binding sequence of the present
10 invention. Alternatively, as shown for instance in Example 6, a ribozyme of the invention can be introduced into a cell directly, i.e., without using a vector.

 These ribozymes of the invention include those comprising the substrate binding sequences listed in Tables 1-5 (SEQ ID NOS: 17-21); NHMCZF-4 (SEQ ID NO:
15 46); listed in Tables 7 and 9 (SEQ ID NOS: 50-72 and 100-112); listed in Table 8 (SEQ ID NOS: 96-97); FA5-VR1 (SEQ ID NO: 134); and FA5-VR5 (SEQ ID NO: 138), and any other hairpin or hammerhead ribozyme comprising a substrate binding sequence designed as described herein and which binds to and cleaves any of the genes disclosed herein, including NHMCZF (GenBank Accession No. AL096880; (SEQ ID NO: 27)),
20 FLJ22165 (GenBank Accession No. AK025818; (SEQ ID NO: 40)), FAPP2 (SEQ ID NO: 42) or human PATZ (SEQ ID NO: 29).

 The present invention also provides amino acid sequences encoded by the nucleic acid sequences disclosed herein. For example, provided is a compound
25 comprising or consisting of SEQ ID NO: 158, which is the amino acid sequence encoded by bases 3-962 of the 4.1 kb contig (SEQ ID NO: 157). Also provided is a compound comprising or consisting of SEQ ID NO: 167, which is the amino acid sequence encoded by bases 1-999 of the 5.5 kb contig (SEQ ID NO: 166). Also provided are compounds that have 80%, 85%, 88%, 90%, 92%, 94%, 95%, 96%, 97%, 98% and, most preferably,

99% amino acid identity with these amino acid sequences (SEQ ID NOS: 158, 167). Additionally provided are compounds that comprise or consist of 25, 20, 15, or 10 or more contiguous amino acids of these amino acid sequences (SEQ ID NOS: 158, 167).

5 The present invention also provides additional amino acid sequences encoded by the nucleic acid sequences disclosed herein. For example, provided is a compound comprising or consisting of SEQ ID NOS: 169, 170 and 171, which are the amino acid sequence encoded by NHMCZF (GenBank Accession No. AL096880; (SEQ ID NO: 27), FAPP2 (SEQ ID NO: 42) and human PATZ (SEQ ID NO: 29), respectively.
10 Also provided are compounds that have 80%, 85%, 88%, 90%, 92%, 94%, 95%, 96%, 97%, 98% and, most preferably, 99% amino acid identity with these amino acid sequences (SEQ ID NOS: 169, 170 or 171). Additionally provided are compounds that comprise or consist of 25, 20, 15, or 10 or more contiguous amino acids of these amino acid sequences (SEQ ID NOS: 169, 170 or 171).

15

The compounds containing the amino acid sequences described above can be used to inhibit induction of apoptosis in a cell. Alternatively, these compounds can be used to identify agents that promote induction of apoptosis in a cell.

20 Accordingly, the present invention provides methods of identifying agents that promote induction of apoptosis in a cell. Such method includes: 1) assessing the binding capability of the agent with a) a target molecule containing an RST of the invention as described herein; or b) a target molecule containing an amino acid sequence described above; and 2) introducing the agent into the cell and measuring the level of
25 apoptosis, where an increase in the level indicates that the agent promotes induction of apoptosis.

In accordance with the present invention, cells that are resistant to apoptosis induction may be rendered susceptible to apoptosis induction by the method

described hereinabove, and the cells may then be contacted with an apoptosis inducing agent so as to induce apoptosis in the cell. This method is particularly useful for treating cancer cells such as leukemia cells, as well as other cancer cells such as bladder brain, lung, colon, pancreatic, breast, ovarian, cervical, liver pancreatic, stomach, lymphatic, prostate and the like. Any of a variety of well-known apoptosis inducing agents can be used for this purpose. A preferred apoptosis inducing agent is one that triggers a “death receptor” type cell surface protein (Baker *et al.* (1996) *Oncogene*. 12:1-9), which includes Fas, TNF-alpha receptor, the TRAIL receptor, and the like. A particularly preferred apoptosis inducing agent is one that triggers the FAS receptor, such as an antibody to the FAS receptor as described in the Examples or soluble FAS ligand (see U.S. Pat. No. 6,042,826 to Caligiuri *et al.*). Other suitable apoptosis inducing agents include adamantyl derivatives (see U.S. Pat. No. 6,127,415 to Pfahl *et al.*), 2-nitroimidazole derivatives (see U.S. Pat. No. 5,929,014 to Ohyama), benzamidine riboside (see U.S. Pat. No. 5,902,792 to Jayaram), branched apogenic peptide (see U.S. Pat. No. 5,591,717 to Rojko *et al.*), chemotherapeutic agents such as 5-FU, cisplatin, vincristine, methotrexate, doxorubicin, and the like.

The present invention also provides a method of facilitating the induction of apoptosis in a cell resistant to induction of apoptosis, comprising reducing the level of a protein expressed in the cell which is involved in inhibiting apoptosis induction, and then contacting the cell with an apoptosis inducing agent, such as the agents described above, to induce the cell to undergo apoptosis. The step of reducing the level of the protein involved in apoptosis inhibition preferably is carried out by reducing the level of the RNA in the cell encoding the protein. In accordance with one embodiment of the present invention, this is accomplished by transducing the cell with an expression vector encoding a ribozyme having a substrate binding sequence that enables the ribozyme to cleave the RNA encoding the protein. Any of the ribozymes disclosed herein, which have been shown to be effective in facilitating the induction of apoptosis, may be used for this purpose.

In accordance with another embodiment of the present invention, the step of reducing the level of the target protein in the cell can be accomplished by contacting the cell with antisense compounds which are complementary to any portion of the
5 substrate binding sequences of the ribozymes disclosed herein.

The antisense compounds that may be used in connection with this embodiment of the present invention preferably comprise between about 8 to about 30 nucleobases (*i.e.*, from about 8 to about 30 linked nucleosides), more preferably from
10 about 12 to about 25 nucleobases, and may be linear or circular in configuration. They may include oligonucleotides containing modified backbones or non-natural internucleoside linkages. Preferred modified oligonucleotide backbones include, for example, phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotriesters, methyl and other alkyl phosphonates
15 including 3'-alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, and boranophosphates having normal 3'-5' linkages, 2'-5' linked analogs of these, and those having inverted polarity wherein the adjacent pairs of
20 nucleoside units are linked 3'-5' to 5'-3' or 2'-5' to 5'-2'. Methods of preparing antisense compounds are well known in the art (see, for example, U.S. Patent No. 6,210,892).

In accordance with yet another embodiment of the present invention, the specific activity of the protein expressed in the cell (such as inhibiting the induction of
25 apoptosis by Fas triggering in DLD-1 colon carcinoma cells) may be reduced further by treating the cell with an agent that binds to the protein and inhibits its activity. Agents suitable for this purpose can be peptides, nucleic acids, organic compounds, and the like. Bioassays for selecting protein binding agents that modulate protein activity are well known in the art (see, *e.g.*, U. S. Patent No. 5,618,720).

The present invention also provides a method of inhibiting the growth of a cancer in a subject, the method comprising administering to the subject an effective amount of an expression vector comprising a sequence of nucleotides that encodes a ribozyme having a substrate binding sequence disclosed herein. The expression vector is preferably administered in combination with a suitable carrier. After the vector has been administered, the ribozyme is expressed in the cells and apoptosis induction facilitated as described herein. The subject may optionally be treated with an apoptosis inducing agent, as disclosed herein, to further induce apoptosis and reduce the growth of the tumor.

10

Administration of the vector or the apoptosis inducing agent can be by any suitable route including oral, sublingual intravenous, subcutaneous, transcutaneous, intramuscular, intracutaneous, and the like. Any of a variety of non-toxic, pharmaceutically acceptable carriers can be used for formulation including, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea, dextrans, and the like. The formulated material may take any of various forms such as injectable solutions, sterile aqueous or non-aqueous solutions, suspensions or emulsions, tablets, capsules, and the like.

20

As used herein, the phrase "effective amount" refers to a dose of the deliverable sufficient to provide circulating concentrations high enough to impart a beneficial effect on the recipient, which is inhibition of cancer growth. With the vector deliverable, the concentration of vector administered should be sufficient to transform enough of the target cells. With the apoptosis inducing deliverable, the concentration should be sufficient to induce apoptosis in a sufficient number of the target cells.

25

The specific therapeutically effective dose level for any particular subject and deliverable depends upon a variety of factors including the disorder being treated, the severity of the disorder, the activity of the specific compound administered, the route of

administration, the rate of clearance of the specific compound, the duration of treatment, the drugs used in combination or coincident with the specific compound, the age, body weight, sex, diet and general health of the patient, and like factors well known in the medical arts and sciences. Dosage levels typically range from about 0.001 up to 100
5 mg/kg/day; with levels in the range of about 0.05 up to 10 mg/kg/day.

Methods for preparing oligonucleotide probes known in the art may be effectively used for preparing the oligonucleotide probes of the present invention. See, for example, Beaucage and Carruthers (1981) *Tetrahedron Lett.* 22:1859-1862; Matteucci
10 *et al.* (1981) *J. Am. Chem. Soc.*, 103:3185; Sambrook *et al.* (1989) *Molecular Cloning: A Laboratory Manual* (2d ed.), Vols. 1-3, Cold Spring Harbor Laboratory; F. Ausubel *et al.* (ed.) (1987) *Current Protocols in Molecular Biology*, Greene Publishing and Wiley-Interscience, New York (1987); Hames and Higgins (eds.) (1985) *Nucleic Acid Hybridization, A Practical Approach*, IRL Press; Gall and Pardue (1969) *Proc. Natl.*
15 *Acad. Sci. USA*, 63:378-383; and John *et al.* (1969) *Nature* 223:582-587.

Typically, the probes used to detect hybridization are labeled to facilitate detection but the target nucleic acid may be labeled instead. Probes or nucleic acid targets may be labeled by any one of several methods typically used to detect the
20 presence of hybridized polynucleotides. The most common method of detection is the use of autoradiography with ^3H , ^{125}I , ^{35}S , ^{14}C , or ^{32}P -labeled probes, or the like. Other labels include ligands which bind to labeled antibodies, fluorophores, chemiluminescent agents, enzymes, and antibodies which can serve as specific binding pair members for a labeled ligand. See, for example, Tijssen, P., "Practice and Theory of Enzyme
25 Immunoassays" in Burdon, R.H., van Knippenberg, P.H. (eds.) (1985) *Laboratory Techniques in Biochemistry and Molecular Biology*, Elsevier, pp. 9-20.

The present invention also provides an antibody with binding specificity for a protein that inhibits the induction of apoptosis; the antibody may also be used to

detect the level or activity of a polypeptide involved in the inhibition to apoptosis induction. In a preferred embodiment, the antibody has binding specificity for a protein or peptide (i.e., amino acid sequence) encoded by the genes or nucleic acid sequences disclosed herein.

5

As used herein, the term "antibody" comprises two heavy chains and two light chains that associate to form two binding sites in each antibody molecule. The term also contemplates fragments of antibodies such as Fab'2 fragments and fragments with a single binding site such as Fab' Fv sFv, and the like. The term includes a monoclonal
10 antibody, a polyclonal antibody, or a collection of polyclonal antibodies such as is present in the antiserum of an immunized animal.

As used herein, the phrase "binding specificity," in relationship to an antibody that binds to a protein or peptide, refers to a binding reaction which is
15 determinative of the presence of the protein in the presence of a heterogeneous population of proteins and other biologics. Thus, under designated immunoassay conditions, the specified antibody binds to a particular protein and does not bind significantly to other proteins present in the sample.

20 Methods of producing polyclonal and monoclonal antibodies are known to those of skill in the art. See, e.g., Coligan (1991) *Current Protocols in Immunology* Wiley/Greene, NY; and Harlow and Lane (1989) *Antibodies: A Laboratory Manual*, Cold Spring Harbor Press, NY; Stites *et al.* (eds.) *Basic and Clinical Immunology* (4th ed.) Lange Medical Publications, Los Altos, CA; Huse *et al.* (1989) *Science* 246:1275-1281;
25 and Ward *et al.* (1989) *Nature* 341:544-546, and references cited therein.

The diagnostic methods described herein are applicable to the identification of cancer cells resistant to apoptosis induction present in, for example, solid

tumors (carcinomas and sarcomas) such as, for example, breast cancer, ovarian cancer and prostate cancer. Such methods include the detection of a nucleic acid encoding a molecular product having an RST identified herein as involved in inhibiting apoptosis induction.

5

Various qualitative and quantitative assays to detect altered expression or structure of a nucleic acid molecule in a sample are well known in the art, and generally involve hybridization of the target sequence to a complementary primer or probe (which may be referred to as a reagent). Such assays include, for example, *in situ* hybridization, which can be used to detect altered chromosomal location of the nucleic acid molecule, altered gene copy number, or altered RNA abundance, depending on the format used. Other assays include, for example, RNA blots and RNase protection assays, which can be used to determine the abundance and integrity of RNA; DNA blots, which can be used to determine the copy number and integrity of DNA; SSCP analysis, which can detect single point mutations in DNA, such as in a PCR or RT-PCR product; and coupled PCR, transcription and translation assays, such as the Protein Truncation Test, in which a mutation in DNA is determined by an altered protein product on an electrophoresis gel. Further assays include methods known in the art for genotyping, for example, by RFLP analysis or by determining specific SNPs. An appropriate assay format and reagent to detect an alteration in the expression or structure of an apoptosis induction resistance regulator nucleic acid molecule can be determined by one skilled in the art depending on the alteration one wishes to identify.

The invention also includes a high throughput drug discovery method using ribozyme transduced cells and chip array technology to identify compounds that modulate apoptosis induction regulatory activity. By combining array technology with ribozyme knockdown, drugs can be rapidly screened for effects on a given pathway. Once the expression profile leading to a given phenotype is determined, additional arrays can be generated with the relevant regulated EST sequences. These can be screened with

mRNA from drug treated cells. Profiles matching the ribozyme treated profile can be identified. Treatment with the drugs identified in this way can be expected to give the desired phenotype.

5 This methodology allows the linking of the function of these target genes to the desired phenotype, *i.e.*, modulation of apoptosis induction. Small molecule drugs, ribozyme drugs, or antibody drugs can be identified by those skilled in the art that inhibit the activity of these gene targets resulting, for example, in reduced resistance to apoptosis induction. The gene targets can be used to develop high throughput assays that can be
10 screened with existing small molecule libraries. In addition, genes which express a surface or secreted protein can be targets for antibody development. Antibodies specific for the gene product can be generated preferably in transgenic mouse systems to generate human antibodies. Furthermore, chimeric ribozyme drugs targeting these apoptosis induction resistance regulators can be designed as explained above.

15 As used herein, "a target molecule responsive to the activity of the apoptosis induction regulator" means that the apoptosis induction regulator either binds or chemically modifies the target molecule that exists in a cell. For example, if the apoptosis induction regulator has DNA binding activity for use in, for example,
20 transcriptional gene regulation, the target molecule responsive to this activity is a nucleic acid comprising a sequence of nucleotides recognized and bound by the particular apoptosis induction regulator. If the apoptosis induction regulator has protein kinase activity, due for example to having a serine/ threonine kinase domain, the target molecule responsive to this activity is a protein having an appropriate serine or threonine kinase
25 recognition site. Likewise, for activity as a protease, the target molecule responsive is a protein cleaved by the apoptosis induction regulator.

When the apoptosis induction regulator activity to be measured for drug screening is DNA binding, such binding can be determined by assaying the expression of

a reporter gene that is operatively linked to the nucleic acid element. In this case, an increase in the amount of expression or activity of the reporter gene in the presence of a test compound compared to the absence of the test compound indicates that the compound has apoptosis induction regulator DNA binding inhibitory activity. The
5 magnitude of the increase in expression activity will correlate with the apoptosis induction regulator inhibitory activity of the test compound. Exemplary reporter genes include apoptosis induction, EGFP and hygromycin resistance gene.

As used herein, the term "nucleic acid element" when used in reference to
10 regulation of apoptosis induction expression refers to a nucleic acid region that modulates apoptosis induction expression. Exemplary nucleic acid elements are the apoptosis induction 5' promoter and regulatory region or other transcriptional regulation regions, and translational regulatory regions of the transcribed mRNA. Generally, the nucleic acid element will be the 5' promoter and regulatory region.

15

Similarly, compounds that increase or enhance the activity of apoptosis induction regulator also can be identified. A test compound added to a sample containing an apoptosis induction regulator and a nucleic acid element modulated by an apoptosis induction regulator which decreases apoptosis induction activity or the amount or rate of
20 expression of apoptosis induction or a reporter gene operatively linked to the nucleic acid element compared to the absence of the test compound indicates that the compound increases the activity of the apoptosis induction regulator. Therefore, the invention provides a method of identifying compounds that modulate the activity of an apoptosis induction regulator.

25

A reaction system for identifying a compound that inhibits or increases apoptosis induction regulator activity can be prepared using essentially any sample, material or components thereof that contains an apoptosis induction regulator. An apoptosis induction regulator containing sample used for such methods can be, for

example, *in vitro* transcription or translation systems using, for example, nucleic acid derived from the apoptosis induction gene-of a normal or tumor cell or a hybrid construct linking the nucleic acid element modulated by an apoptosis induction regulator to a reporter gene. Alternatively, nucleic acids and proteins obtained from normal cells can
5 also be used since apoptosis induction regulators can also act in normal cells. The apoptosis induction regulator-containing sample can additionally be derived from cell extracts, cell fractions or, for example, *in vivo* systems such as cell culture or animal models which contain a nucleic acid element modulated by an apoptosis induction regulator. The expression levels or activity of apoptosis induction or the reporter gene
10 can be measured in the reaction system to determine the modulatory effect of the test compound on the apoptosis induction regulator. Such measurements can be determined using methods described herein as well as methods well known to those skilled in the art.

Briefly, the apoptosis induction regulator source is combined with a
15 nucleic acid element or protein modulated by an apoptosis induction regulator as described above and incubated in the presence or absence of a test compound. The expression levels or activity of apoptosis induction or the reporter gene in the presence of the test compound is compared with that in the absence of the test compound. Those test compounds which provide an increase in expression levels or activity of apoptosis
20 induction or the reporter gene of at least about 20% are considered to be apoptosis induction regulator activators, or agonists, and are potential therapeutic compounds for the treatment of neoplastic diseases such as cancer. Similarly, those compounds which decrease expression levels or activity of apoptosis induction regulator or the reporter gene by about 20% or more are considered to be compounds which decrease the activity of an
25 apoptosis induction regulator, or apoptosis induction regulator antagonists. Such antagonists can be used as therapeutics, for example, to promote cell growth or cell survival in transplanted or explanted cells which are subsequently transplanted. Compounds identified to modulate apoptosis induction regulator activity can, if desired, be subjected to further *in vitro* or *in vivo* studies to corroborate that they affect the

activity of an apoptosis induction regulator toward the apoptosis induction expression or activity.

Suitable test compounds for the above-described assays can be any
5 substance, molecule, compound, mixture of molecules or compounds, or any other composition which is suspected of being capable of inhibiting apoptosis induction regulator activity *in vivo* or *in vitro*, for example, compounds with cell proliferation-inhibiting activity. The test compounds can be macromolecules, such as biological
10 polymers, including proteins, polysaccharides and nucleic acids. Sources of test compounds which can be screened for apoptosis induction regulator inhibitory activity include, for example, libraries of small organic molecules, peptides, polypeptides, DNA, and RNA. Additionally, test compounds can be pre-selected based on a variety of criteria. For example, suitable test compounds can be selected as having known inhibition or enhancement activity with respect to cell proliferation. Alternatively, the test compounds
15 can be selected randomly and tested by the screening methods of the present invention. Test compounds can be administered to the reaction system at a single concentration or, alternatively, at a range of concentrations to determine, for example, the optimal modulatory activity toward the apoptosis induction regulator.

20 The activity of an apoptosis induction regulator for which drug screening is desired can be a protein kinase activity. For example, apoptosis induction regulators that have a serine/threonine kinase domain may be used for drug screening where the activity which is modulated is a protein kinase activity. Protein kinase assays are well known to those skilled in the art (see, *e.g.*, U.S. Pat. Nos. 5,538,858 and 5,757,787; Anal.
25 Biochem, 209:348-353, (1993)).

The activity of an apoptosis induction regulator for which drug screening is desired also can be GTP binding activity. For example, apoptosis induction regulators that have a GTP binding site may be used for drug screening where the activity which is

modulated is GTP binding. Apoptosis induction regulators that have GTP-binding activity may regulate cell growth such as through regulating apoptosis induction expression, or may have affects on cell cycle control, protein secretion, and intracellular vesicle interaction. GTP binding assays are well known to those skilled in the art (see,
5 *e.g.*, U.S. Pat. Nos. 5,840,969 to Hillman et al.).

The activity of an apoptosis induction regulator for which drug screening is desired also can be hormone binding activity. For example, apoptosis induction regulators that have a hormone binding site may be used for drug screening where the
10 activity which is modulated is hormone binding. Hormones that bind to an apoptosis induction regulator may be steroid hormones such as estrogen or a protein based hormone. Receptor hormone binding assays including receptor estrogen binding assays are well known to those skilled in the art (see, *e.g.*, U.S. Pat. Nos. 6,204,067 to Simon et al.).

15

The present invention also provides kits for carrying out the methods of the present invention. Such kits include one or more reagents of the invention such as antibodies or oligonucleotide probes specific for polypeptides or genes, respectively, involved in inhibition of apoptosis induction. Such agents may be detectably labeled
20 using an appropriate enzyme, dye, radioisotope, and the like. The kits also may include additional reagents specific for binding to the reagents of the invention as well as necessary chemicals and buffers.

The following examples are intended to illustrate but not limit the present
25 invention.

EXAMPLES

Example 1: Preparation of a Retroviral Random Ribozyme Gene Vector Library

This example describes the preparation of a retroviral random ribozyme gene vector library, the first step in the method for selecting and identifying ribozymes having substrate recognition sequences involved in facilitating apoptosis induction. The library was prepared essentially as described in W0 00/05415 (Barber *et al.*). The plasmid-based retroviral ribozyme library was created in vector pLPR. Vector pLPR-1kb contains: 1) 5' and 3' long terminal repeats (LTR) of the Moloney retroviral genome; 2) transcription cassette for the ribozyme genes via tRNA^{Aval} promoter with a 1 kb stuffer insert at the site intended for the ribozyme gene; and 3) SV40 promoter driving puromycin resistance. In this design, the stuffer insert was removed and replaced by the random ribozyme library insert, with transcription under control of the tRNA^{Aval} promoter.

15

The pLPR-1kb vector (see Figure 3) was prepared by digesting plasmid pLPR overnight at 37°C with BamH1, phenol:chloroform extracted and ethanol precipitated. The resuspended DNA was then digested overnight at 37°C with MluI. This double digestion excises the 1kb stuffer fragment. The resultant 6kb plasmid vector DNA fragment was purified by agarose gel electrophoresis.

20

The random ribozyme library inserts were prepared from three oligonucleotides, which were synthesized and annealed in annealing buffer (50 mM NaCl, 10 mM Tris pH 7.5, 5 mM MgCl₂) at a molar ratio of 1:3:3 (oligo1:oligo2:oligo3) by heating to 90°C followed by slow cooling to room temperature. The three oligonucleotides had the following sequences:

25

Oligo1:

5'-pCGCGTACCAGGTAATATACCACGGACCGAAGTCCGTGTGTTT
CTCTGGTNNNNTTCTNNNNNNNNNGGATCCTGTTTCCGCCCCGGTTT-3'
(SEQ ID NO: 11)

5

Oligo2: 5'-pGTCCGTGGTATATTACCTGGTA-3' (SEQ ID NO: 12)

Oligo3: 5'-pCGAAACCGGGCGGAAACAGG-3' (SEQ ID NO: 13)

10

Random incorporation of A, T, C and G nucleotides at the positions represented as N in oligo1, was achieved by premixing A, T, C and G reagents at every N position in the oligonucleotide synthesis. The ribozyme insert library formed by annealing the three oligonucleotides (SEQ ID NOS: 11, 12, 13) thus contains 8 positions with random nucleotides corresponding to helix 1 of the ribozyme, and 4 random positions with random nucleotides corresponding to helix 2 of the ribozyme (see Figure 1).

15

A pLPR-1kb vector DNA fragment was ligated overnight to the random ribozyme insert library using 0.5 pmole of the vector, an 8-fold molar excess of annealed oligonucleotides and 10 units of T4 DNA ligase. The resulting library of vectors, designated pLPR-library were electroporated into ultracompetent DH12S bacteria. A total of 5×10^7 bacterial colonies containing the retroviral plasmid ribozyme library were obtained.

20

25

Bacterial colonies containing the retroviral plasmid ribozyme library were pooled in aliquots as a master stock and frozen at -80°C. Working stocks were made by culturing 1 ml of the master stock in 60 ml LB media overnight at 30°C. A 1 ml aliquot of the working stock was used to make a 500 ml bacterial culture by incubation at 30°C overnight. Retroviral DNA was then extracted from the 500 ml culture and used to prepare viral vector for the library selection.

30

A viral vector was produced from the ribozyme library plasmid using a triple transfection technique. In this approach, CF2 cells were seeded at a concentration of 3.5×10^4 cells/cm². The next day, 2.2×10^8 CF2 cells were incubated for 6 hours in 665 ml of serum-free medium transfection media containing 20 mg of a triple plasmid mixture complexed with 12 ml of a cationic lipid (TransIT-LT1; Pan Vera Corporation). The plasmid mixture contained a 2:3:1 ratio of the ribozyme gene library plasmid (or control ribozyme plasmid), a plasmid encoding the moloney-murine virus gag-pol genes, and a plasmid encoding the vesicular stomatitis virus-G gene. Cell supernatant containing retroviral particles was collected every 24 hours beginning on day 2 following transfection. The viral containing supernatant was filtered through 0.4 μ m filters and titred in a standard assay using HT1080 cells (see WO 00/05415 to Barber *et al.*).

Following the cloning of the randomized hairpin ribozyme genes into pLPR, the "randomness" of the plasmid library was evaluated as described in WO 00/05415 to Barber *et al.* The frequencies of the four nucleotides, with 95% confidence limits, in the random positions were calculated to be G: 22.3 ± 6.1 , A: 31.9 ± 7.0 , T: 27.3 ± 7.8 and C: 18.01 ± 15.1 . Since the expected frequency for each base is 25%, each base appears to be randomly represented (except for C, which may be slightly lower than expected). These variations most likely result from the unbalanced incorporation of nucleotides during the chemical synthesis of the oligonucleotides and could reduce the complexity of the library.

For a functional evaluation of the library's complexity, *in vitro* cleavage was utilized to determine if ribozymes that target known RNA substrates were present in the library pool. This involved *in vitro* transcribing of the entire ribozyme library in one reaction and then testing the pool's ability to cleave a variety of different RNA substrates of both cellular and viral origin. Six out of seven known RNA targets were properly and efficiently cleaved by the *in vitro* transcribed library. This qualitative analysis suggested a significantly complex library of ribozyme genes and the lack of cleavage of one target

out of seven may reflect the slight non-randomness suggested by the base composition described above.

Example 2: Introduction of the Random Ribozyme Gene Vector Library into
5 *Mammalian Cells and Selection of Apoptosis Induction Relevant Nucleotide Sequences*

This example describes a method for identifying ribozymes involved in apoptosis induction. The pLPR-library vector described in Example 1 and a control vector, pLPR-TL3, were used to transduce DLD-1 colon carcinoma cells (ATCC,
10 Bethesda MD). The control vector differs from the pLPR-library vector (see Figure 2) in having an HCV ribozyme control gene in place of the ribozyme library gene.

For transduction, DLD-1 cells were grown to about 70% confluency in T225 flasks (about 6×10^7 cells). Transduction of the cells was accomplished by
15 incubating them for 24 hours at 37°C with retroviral vector coding for the library at a multiplicity of infection (MOI) of 1.

After incubation with retroviral vector, the transduction medium was removed by aspiration and replaced with growth medium containing puromycin (2
20 µg/ml). The next day, cells were re-fed with media containing 2 µg/ml puromycin. The cells were maintained in selection medium for 10-14 days in order to select for stable integration of the retroviral vector. During the course of this selection the cells were re-fed every three days.

25 After stable selection, the cells were subjected to induction of apoptosis by incubation for 18 hours with purified IgM ligating antibody to CD95 (clone 11, PanVera) added at 160 ng/ml. Apoptotic cells were then identified by a dual staining protocol. In a first step, following induction, cells were removed by trypsin, washed 2x with PBS, suspended in binding buffer and then stained with Annexin-V-FITC/PI, essentially as

described by the manufacturer (Boehringer/Manheim). Annexin-V binds to phosphatidyl serine, which translocates from the inner cell membrane space to the outer cell membrane surface early in apoptosis. Concurrent staining with propidium iodide (PI), a DNA stain, also was used to identify and exclude necrotic cells from the population of cells
5 undergoing apoptosis.

Subsequently, the TUNEL assay (Roche), which is believed to provide less variability in the identification of apoptotic cells, was used. Following staining (or TUNEL), the cells were subjected to separation by fluorescence activated cell sorting
10 (FACS). Genomic DNA was isolated from the FACS sorted Annexin-V positive/PI negative or the TUNEL positive cells and the ribozyme genes were then rescued by PCR amplification of the DNA.

Ribozyme genes were rescued from the FACS selected cell population by
15 PCR rescue, which was performed on five separate aliquots of 1 µg of genomic DNA extracted from the cells using the QIAmp Blood Kit (Qiagen, Valencia, CA). PCR was carried out using the AmpliTaq Gold system (Perkin-Elmer, Norwalk, CT) with an initial denaturation at 94°C for 10 min. followed by 35 cycles of 94°C for 20 sec., 65°C for 30 sec., and 72°C for 30 sec. A final extension was performed at 72°C for 7 min. PCR
20 primers, 5'-GGCGGGACTATGGTTGCTGACTAAT-3' (SEQ ID NO: 14) and 5'-GGTTATCACGTTTCGCCTCACACGC-3' (SEQ ID NO: 15) annealing within the vector amplified a 300 bp fragment containing the ribozyme genes. The pooled PCR product, which contained a pool of ribozyme genes, was isolated by electrophoresis on 1% agarose, purified using a Gel Extraction Kit (Qiagen), then digested with BamHI and
25 MluI and ligated into vector pLPR digested with the same enzymes. The ligated DNA was used to transform DH12S *E. coli* bacteria by electroporation. The entire bacterial culture was plated on LB-agar plates containing ampicillin and incubated at 37°C overnight. The resulting bacterial colonies were pooled and purified DNA was used in a triple transfection protocol (as described above in Example 1) to produce retroviral

vector. Individual colonies were also sequenced by the standard dideoxy method using a vector primer 5'-CTGACTCCATCGAGCCAGTGTAGAG-3' (SEQ ID NO: 16).

Three rounds of successive vector transduction, apoptosis induction,
 5 FACS selection and ribozyme gene rescue were performed. The third round of FACS selection showed that approximately 5-6% of the pLPR-library transduced cells had entered apoptosis as compared to 1-2% for the control vector. These results indicate that progressive selection of library transduced cells enriched the ribozyme pool for ribozymes that facilitate apoptosis.

10

Analysis of the ribozyme gene inserts following the third round of PCR rescue indicated enrichment of several ribozyme substrate binding sequences. Five predominant ribozyme substrate binding sequences designated RAP2 (SEQ ID NO: 17), RAP4 (SEQ ID NO: 18), RAP6 (SEQ ID NO: 19), RAP10 (SEQ ID NO: 20) and
 15 RAP594 (SEQ ID NO: 21) were identified. The substrate binding sequences of each of these identified ribozymes is listed in the first row of Tables 1-5.

Table 1: RAP2 Substrate Binding Sequence and complementary RST

RAP2: substrate binding sequence	5'- CCAGTCCA AGAA GACC – 3' (SEQ ID NO: 17)
RAP2: complementary RST	5' - GGTC NGTC TGGACTGG – 3' (SEQ ID NO: 22)

20

Table 2: RAP4 Substrate Binding Sequence and complementary RST

RAP4: substrate binding sequence	5'- TCGTTGTG AGAA AGCC – 3' (SEQ ID NO: 18)
RAP4: complementary RST	5' – GGCT NGTC CACAACGA – 3' (SEQ ID NO: 23)

25

Table 3: RAP6 Substrate Binding Sequence and complementary RST

RAP6: Substrate binding sequence	5'- GTCTTCAT AGAA GGCC – 3' (SEQ ID NO: 19)
RAP6: Complementary RST	5' – GGCC NGTC ATGAAGAC – 3' (SEQ ID NO: 24)

Table 4: RAP10 Substrate Binding Sequence and complementary RST

RAP10: Substrate binding sequence	5'- TGATCCGT AGAA CATA – 3' (SEQ ID NO:20)
RAP10: Complementary RST	5' - TATG NGTC ACGGATCA – 3' (SEQ ID NO: 25)

5

Table 5: RAP594 Substrate Binding Sequence and complementary RST

RAP594: Substrate binding sequence	5'- TATGCTGT AGAA ATAA – 3' (SEQ ID NO:21)
RAP594: Complementary RST	5' - TTAT NGTC ACAGCATA – 3' (SEQ ID NO: 26)

10

The validity of individual library-selected ribozymes for facilitating apoptosis induction was determined by transfection of DLD-1 cells followed by analysis of apoptosis induction. For this purpose, nucleic acid sequence encoding ribozymes having the RAP sequences shown in Tables 1-5 were cloned into pLPR in place of the 1kb stuffer. Vector LPR-TL3 was used as a control.

15

For transfection, DLD-1 cells were grown to about 70% confluency in T75 flasks (about 5×10^6 cells). The media was then removed and replaced with 0.8 ml of serum free Opti-MEM media (GIBCO). The cells were incubated for four hours at 37°C with complexes containing a lipid-plasmid DNA complex.

20

The lipid-plasmid DNA complex was prepared by combining lipid reagent lipofectamine (GIBCO) at a ratio of 4 microliters lipid reagent to 1 microgram DNA (single ribozyme encoding or control LPR-TL3). Lipid/ DNA complexes were allowed to form for 20 min. at room temperature before use.

After incubation of the cells with the complexes, the transfection medium was removed by aspiration and replaced with complete growth medium. The cells were cultured for 24 hrs before selection in growth medium containing puromycin (2 µg/ml). The next day, cells were re-fed with media containing 2 µg/ml puromycin. The cells
5 were allowed to recover and expand for two weeks.

The cells were then tested for the ability to undergo apoptosis upon induction with CD95 ligating antibody. In all cases, transfection with the vector encoding ribozymes with the individual library-selected substrate binding sequences
10 confirmed the previously observed phenotype -- an increase in induction of apoptosis (10-20% of the transfected/selected DLD-1 cell population).

Example 3: Identification of Genes Involved in Inhibition of Apoptosis Induction

15 This example describes methods to identify cellular genes involved in inhibiting cells to the induction of apoptosis by the CD95 antibody. Since ribozymes recognize their cognate targets by sequence complementarity, the substrate binding sequence of a ribozyme which is associated with a particular phenotype can be used to define a ribozyme sequence tag (RST) that is present in a target gene involved in the
20 phenotype. In the ribozyme library used herein, the RST is 16 bases long, comprising the two target binding arms (helix 1 and 2) surrounding the requisite NGUC in the target (see Figure 1).

The second row of Tables 1-5 above show the complementary RST (SEQ
25 ID NOS: 22-26) for each library-derived substrate binding sequence. In each case, the first four bases (5' end) representing the Helix 2 sequence and the last eight bases representing the Helix 1 sequence are the direct Watson-Crick base complement to the corresponding substrate binding sequence. The base at the fifth position from the 5' end of the RST need not be specified and is shown as an "N." The three bases located 3' to

the “N” in the RSTs represent the gene sequence GTC, which following transcription, becomes the requisite cognate sequence GUC, recognized by “GUC ribozymes” (see Figure 1).

5 To identify genes involved in inhibition to apoptosis induction by CD95 antibody, the gene and expressed sequence tag (EST) public databases were searched using the Basic Local Alignment Search Tool (“BLAST”) (<http://www.ncbi.nlm.nih.gov/BLAST/>) for the presence of the RSTs shown in Tables 1-5. The parameters of the BLAST search were “word size” = 7 and “expected” = 1,000.
10 Four searches were done for each RST using A, T, C, or G in the “N” of the NGUC sequence of the RST.

BLAST searching of the RAP4-RST and RAP10-RST did not yield any substantive results (only incomplete matches with non-human sequences). In contrast,
15 the BLAST search of the RAP2-RST and the RAP6-RST identified several completely matching sequences in the public databases, and the BLAST search of the RAP594-RST identified two separate 15/16 nucleotide matches.

The RAP6-RST perfectly matched a sequence within the NHMCZF gene
20 (GenBank Accession No. AL096880) (SEQ ID NO: 27) located in the nr (non-redundant) database. The NHMCZF gene (entitled “Novel Human mRNA Containing Zinc Finger CH2 Domains”) has a high degree of identity to the mouse MAZR (SEQ ID NO: 28) and human PATZ (SEQ ID NO: 29) gene sequences, also located in the nr database. The RAP6-RST also perfectly matched a sequence within the EST gi:874139
25 (GenBank Accession No. H09317) (SEQ ID No: 30), referred to hereinafter as EST6.

The RAP2-RST was found to perfectly match the a sequence within EST fragment yf56a06.r1 (GenBank Accession No. R12420) (SEQ ID NO: 31), referred to

hereinafter as EST2. Subsequent BLAST searches yielded perfect matches to sequences within eight other EST fragments:

5 602318810F1 (GenBank Accession No. BG116747) (SEQ ID NO: 32);
 602317343F1 (GenBank Accession No. BG115920) (SEQ ID NO: 33);
 602281666F1 (GenBank Accession No. BG111236) (SEQ ID NO: 34);
 602248984F1 (GenBank Accession No. BF692624) (SEQ ID NO: 35);
 601434123F1 (GenBank Accession No. BE892951) (SEQ ID NO: 36);
 10 DKFZp761o0715 (GenBank Accession No. AL138059) (SEQ ID NO: 37);
 cr22e03 (GenBank Accession No. AI754258) (SEQ ID NO: 38); and
 zw05h03 (GenBank Accession No. AA495929) (SEQ ID NO: 39).

As described below in Example 6, it was subsequently determined that EST2 and the eight additional EST fragments described above are overlapping fragments
 15 of the putative cDNA FLJ22165 (GenBank Accession No. AK025818 (SEQ ID NO: 40)).

The RAP594-RST matched 15/16 nucleotides of two gene sequences in the nr database. One of the matches was to CSNK2A1 (GENBANK Accession No. NM_001895.1) (SEQ ID NO: 41) and the other was to FAPP2 (GENBANK Accession
 20 No. NM_032639) (SEQ ID NO: 42).

The involvement of the NHMCZF gene (SEQ ID NO: 27) in inhibiting apoptosis induction with CD95 ligating antibody was confirmed as follows: The nucleotide sequence of the NHMCZF gene was inspected to determine if other segments
 25 of the gene might serve as additional RST sites, and “validation ribozymes” having substrate binding sites complementary to six of these putative RSTs were engineered, as listed in Table 6 below.

Table 6: Validation Ribozyme Substrate Binding Sequences for NHMCZF Gene

Validation Ribozyme	Ribozyme Substrate Binding Sequence (Based on the NHMCZF Gene)
NHMCZF-1	5'-AGCAGCCA AGAA GGCC-3' (SEQ ID NO: 43)
NHMCZF-2	5'-TGAACACC AGAA CAAA-3' (SEQ ID NO: 44)
NHMCZF-3	5'-ATCAGCCG AGAA CCCG-3' (SEQ ID NO: 45)
NHMCZF-4	5'-CCCCATCA AGAA CCAT-3' (SEQ ID NO: 46)
NHMCZF-5	5'-ACCCAAAG AGAA CGAG-3' (SEQ ID NO: 47)
NHMCZF-6	5'-CAAATGCC AGAA GAAC-3' (SEQ ID NO: 48)

5 Retroviral expression plasmids encoding ribozymes having the substrate binding sequences shown in Table 6 were then generated, and DLD-1 cells were tested for CD95 apoptosis induction following transfection with the vectors, as described in Examples 1 and 2. One of these, NHMCZF-4 (SEQ ID NO: 46), whose complementary RST is ATGGAGTCTGATGGGG (SEQ ID NO: 49), bestowed the phenotype of facilitating induction of apoptosis by CD95 ligating antibody. This confirmed the original finding based upon RAP6 that the NHMZCF gene was involved in the inhibition of apoptosis.

Additional RSTs for the NHMZCF gene and the complementary ribozyme substrate binding sites are provided in Table 7 below:

15 Table 7: Additional Ribozyme Substrate Binding Sequences and Target RSTs for NHMZCF

Ribozyme Substrate Binding Sequence (5'-3')	NHMZCF Target RST (5'-3')
GTACGTTG AGAA GTTT (SEQ ID NO: 50)	AAAC AGTC CAACGTAC (SEQ ID NO: 73)
CCCCTGGG AGAA CAAA (SEQ ID NO: 51)	TTTG GGTC CCCAGGGG (SEQ ID NO: 74)
ACCACATA AGAA GCAT (SEQ ID NO: 52)	ATGC GGTC TATGTGGT (SEQ ID NO: 75)
AGGCTGGT AGAA CCGT (SEQ ID NO: 53)	ACGG TGTC ACCAGCCT (SEQ ID NO: 76)
CAGAGTGG AGAA GCTT (SEQ ID NO: 54)	AAGC TGTC CCACTCTG (SEQ ID NO: 77)

CATCATGG AGAA GCAC (SEQ ID NO: 55)	GTGC GGTC CCATGATG (SEQ ID NO: 78)
TGCCCACG AGAA CATG (SEQ ID NO: 56)	GATG GGTC CGTGGGCA (SEQ ID NO: 79)
GCAGGTCT AGAA CTTG (SEQ ID NO: 57)	CAAG TGTC AGACCTGC (SEQ ID NO: 80)
GGAGCGCA AGAA GTCT (SEQ ID NO: 58)	AGAC CGTC TGCCTCC (SEQ ID NO: 81)
TTTTTGGG AGAA GCCA (SEQ ID NO: 59)	TGGC AGTC CCCAAAAA (SEQ ID NO: 82)
CGAGGAGA AGAA TGTT (SEQ ID NO: 60)	AACA TGTC TCTCCTCG (SEQ ID NO: 83)
CTAAAGAT AGAA CAAA (SEQ ID NO: 61)	TTTG CGTC ATCTTTAG (SEQ ID NO: 84)
TCCGTGGG AGAA CAGC (SEQ ID NO: 62)	GCTG TGTC CCCACGGA (SEQ ID NO: 85)
TTTCTAAA AGAA ATTG (SEQ ID NO: 63)	CAAT GGTC TTTAGAAA (SEQ ID NO: 86)
GAAACTGG AGAA GGTT (SEQ ID NO: 64)	AACC AGTC CCAGTTTC (SEQ ID NO: 87)
TGGGAGGG AGAA AAAA (SEQ ID NO: 65)	TTTT GGTC CCCTCCCA (SEQ ID NO: 88)
GGGAGGAT AGAA AACT (SEQ ID NO: 66)	AGTT CGTCA TCCTCCC (SEQ ID NO: 89)
TAGGTGGA AGAA CTAG (SEQ ID NO: 67)	CTAG GGTC TCCACCTA (SEQ ID NO: 90)
TCTTGGAG AGAA CTCA (SEQ ID NO: 68)	TGAG TGTC CTCCAAGA (SEQ ID NO: 91)
TAATGTGT AGAA GCGG (SEQ ID NO: 69)	CCGC AGTC ACACATTA (SEQ ID NO: 92)
CCTGACCA AGAA GGCA (SEQ ID NO: 70)	TGCC AGTC TGGTCAGG (SEQ ID NO: 93)
ACTTCCCT AGAA AGAC (SEQ ID NO: 71)	GTCT GGTC AGGGAAGT (SEQ ID NO: 94)
TCACATGT AGAA CAAC (SEQ ID NO: 72)	GTTG TGTC ACATGTGA (SEQ ID NO: 95)

To confirm the involvement of the EST2 clone (SEQ ID NO: 31) in the inhibition of apoptosis, “validation ribozymes” were engineered, having the substrate

5 binding sequences listed in Table 8 below:

Table 8: Validation Ribozyme Sequences for EST2

Validation ribozyme	Substrate Binding Sequence
Est2-1	5'-TCCTCCCC AGAA CCCT-3' (SEQ ID NO: 96)
Est2-2	5'-TCCAGACA AGAA AGCT-3' (SEQ ID NO: 97)

- 5 Retroviral expression plasmids encoding ribozymes having the substrate binding sequences shown in Table 8 were then generated, and DLD-1 cells were tested for CD95 triggered apoptosis induction following transfection with the plasmids, as described in Examples 1 and 2 above. Both "validation ribozymes" bestowed the phenotype of facilitating apoptosis induction. Their complementary RST sequences are SEQ ID NOS:
- 10 98 and 99, respectively. This confirmed the original finding based upon RAP2 that EST2 was involved in apoptosis inhibition.

Additional RSTs for the EST2 gene and the complementary ribozyme substrate binding sites, based upon the overlap with FLJ22165 (SEQ ID NO: 40) are

15 provided in Table 9 below:

Table 9: Ribozyme Substrate Binding Sequences and Target RSTs for cDNA fragment FLJ22165

Ribozyme Substrate Binding Sequence (5'-3')	FLJ22165 Target RST (5'-3')
CTGACAAA AGAA GTCT (SEQ ID NO: 100)	AGAC AGTC TTTGTCAG (SEQ ID NO: 113)
GTAATTCT AGAA AAGA (SEQ ID NO: 101)	TCTT TGTC AGAATTAC (SEQ ID NO: 114)
TGTATTGA AGAA GAAA (SEQ ID NO: 102)	TTTC TGTC TCAATACA (SEQ ID NO: 115)
CCACATAA AGAA GGAA (SEQ ID NO: 103)	TTCC TGTC TTATGTGG (SEQ ID NO: 116)
CAAGCCCA AGAA AAAA (SEQ ID NO: 104)	TTTT TGTC TGGGCTTG (SEQ ID NO: 117)
CACTGCTA AGAA AGCC (SEQ ID NO: 105)	GGCT TGTC TAGCAGTG (SEQ ID NO: 118)

AGGCAACA AGAA AAAT (SEQ ID NO: 106)	ATTT AGTC TGTTGCCT (SEQ ID NO: 119)
CAACCTGT AGAA AGAG (SEQ ID NO: 107)	CTCT TGTC ACAGGTTG (SEQ ID NO: 120)
AGTCCAAT AGAA GCCA (SEQ ID NO: 108)	TGGC TGTC ATTGGACT (SEQ ID NO: 121)
TTTCCTGA AGAA CTTG (SEQ ID NO: 109)	CAAG AGTC TCAGGAAA (SEQ ID NO: 122)
CCTCAAGA AGAA CACC (SEQ ID NO: 110)	GGTG GGTC TCTTGAGG (SEQ ID NO: 123)
TTAGTAGA AGAA GGGT (SEQ ID NO: 111)	ACCC TGTC TCTACTAA (SEQ ID NO: 124)
AGTGCAGT AGAA CGAT (SEQ ID NO: 112)	ATCG TGTC ACTGCACT (SEQ ID NO: 125)

Similarly, to confirm the involvement of the EST6 clone in apoptosis inhibition, “validation ribozymes” having the substrate binding sequences listed in Table 10 below were engineered against EST6, and DLD-1 cells were transfected with retroviral expression plasmids encoding for these ribozymes. However, in this case, neither of the “validation ribozymes” bestowed the phenotype of facilitating apoptosis induction, and the involvement of EST6 in this process was not confirmed.

Table 10: Validation Ribozyme Sequences for EST6

Validation ribozyme	Substrate Binding Sequence
Est6-1	5'-ATACCCCT AGAA CTGA-3' (SEQ ID NO: 126)
Est6-3	5'-ACATGTAG AGAA CGCA-3' (SEQ ID NO: 127)

In order to determine which of the two BLAST matches to RAP594 -- CSNK2A1 (SEQ ID NO: 41) or FAPP2 (SEQ ID NO: 42) was the correct match, “validation ribozymes” having the substrate binding sequences listed in Table 11 below were engineered against CSNK2A1, and “validation ribozymes” having the substrate binding sequences listed in Table 12 below were engineered against FAPP2:

Table 11: Validation Ribozyme sequences for CSNK2A1

Validation Ribozyme	Substrate Binding Sequence
HRVG-TV130	GGTTGGCG AGAA AAGC (SEQ ID NO: 128)
HRVG-TV 229	CCACATGT AGAA CGTA (SEQ ID NO: 129)
HRVG-TV 463	GGGTTCGT AGAA CAGG (SEQ ID NO: 130)
HRVG-TV 1001	TCACTGTG AGAA AAGC (SEQ ID NO: 131)
HRVG-TV 1711	AAGTGTGG AGAA GTGG (SEQ ID NO: 132)
HRVG-TV2094	AGGGAAAA AGAA AAGG (SEQ ID NO: 133)

Table 12: Validation Ribozyme Sequences for FAPP2

Validation Ribozyme	Substrate Binding Sequence
FA5-VR1	ATTTCACA AGAA GCCA (SEQ ID NO: 134)
FA5-VR2	CAGAATTG AGAA CACC (SEQ ID NO: 135)
FA5-VR3	TCTTGCTG AGAA TGAG (SEQ ID NO: 136)
FA5-VR4	AAATTTGA AGAATCTC (SEQ ID NO: 137)
FA5-VR5	TTAGATT AGAA ACTT (SEQ ID NO: 138)
FA5-VR6	TCCAGTTT AGAATTGG (SEQ ID NO: 139)

- 5 DLD-1 cells were then transfected with retroviral expression plasmids encoding for these ribozymes, and the cells were assayed for their ability to undergo Fas-mediated apoptosis. None of the target validation ribozymes listed in Table 11 was able to confer sensitivity to Fas-mediated apoptosis in DLD-1 cells. However, both FA5-VR1 and FA5-VR5 were able to cause the DLD-1 to undergo apoptosis after induction by Fas. The
- 10 complementary RST sequences of these two validation ribozymes are SEQ ID NOS: 140 and 141, respectively. This confirmed that the FAPP2 gene was the target of RAP594 and that RAP594 was involved in apoptosis inhibition.

Example 4: Confirmation of Target Knockdown

This example describes a method for confirming knockdown, or decrease in the level, of an RNA target identified by the methods described in the previous examples. DLD-1 cells were transfected with either a control plasmid (LPR-TL3) or retroviral plasmids expressing the RAP2 or EST2-1 ribozyme genes. Transfections and selection in puromycin were carried out as described above. Total RNA was extracted from the cells using the RNEASY kit (Qiagen). The RNA was analyzed by TaqMan real time RT-PCR, with the EST2 sequence used as the template to design the TaqMan probe (SEQ ID NO: 142) and primer set (SEQ ID NOS: 143 and 144). Five μ g of total RNA from the cellular samples was used for the analysis. LPR-TL3 was used as the control. The results showed that the RAP2 ribozyme (SEQ ID NO: 17) and the “validation ribozyme” RTV2-1, also known as TV 2-1 or the Est2-1 validation ribozyme (SEQ ID NO: 96), caused a significant knockdown, or decrease in the mRNA, of the EST2 target gene, a 30% decrease using the RAP2 ribozyme (SEQ ID NO: 17) and the a 20% decrease using the Est2-1 (SEQ ID NO: 96) (see Figure 6).

Example 5: Confirmation of Cellular Expression of RNA Target

This example describes a method for confirming that a partial gene sequence identified in Example 3 above, EST2 (SEQ ID NO: 31), is part of a larger mRNA that is normally expressed both in both tumor cell lines and normal tissue. Messenger RNA was prepared from five colon carcinoma cell lines: DLD-1; SW480; HT-29; Colo 220; SW1417. The RNA was prepared using the RNEASY kit and oligo dT (Qiagen). Messenger RNA from normal colon tissue was purchased (ResGen/Invitrogen) and prepared. One μ g of mRNA was loaded onto a 1% agarose gel for each sample. Northern blot and radioactive probing of the blot was done by protocols known to those skilled in the art. The probe was generated by PCR using EST2 (SEQ ID NO: 31) as the template and primers TV2-R (SEQ ID NO: 143) and EST2ProbeF (SEQ ID NO: 145).

The blot was able to detect a single band, approximately 7-7.5 kb in length, present in both the cell lines and the normal colon tissue (see Figure 7). This indicates that the EST2 (SEQ ID NO: 31) sequence is part of a larger mRNA that is expressed both in tumor cell lines and normal tissue.

5

Example 6: Isolation, assembly and sequence of a full-length cDNA for EST2 Gene

This example describes the process of assembling the full-length cDNA for the gene that contains the EST2 fragment identified in Example 3 above. Utilizing the CAP contig assembly program (Indiana University Bioarchive), an initial contig was built from the overlapping cDNA FLJ22165 (SEQ ID NO: 40) and the 9 ESTs (SEQ ID NOS: 31-39) that matched the RAP2 RST (SEQ ID NO: 22). The size of this initial contig sequence (SEQ ID NO: 146) was approximately 1.7 kb. Using this contig fragment as the query sequence, a BLAST search was carried out which identified the overlapping EST sequence 601486342F1 (GenBank Accession No. BE877775) (SEQ ID NO: 147), and that extended the 5' end of the contig to a total of about 2 kb (SEQ ID NO: 148).

With the above contig as a guide and template for primer design, RACE (Rapid Amplification of cDNA Ends) was undertaken to isolate and clone the full-length gene. The initial RACE protocol was performed on both colon and placental mRNA samples (ResGen/Invitrogen) using the SMART RACE kit (Clontech). The primer used to initiate the reverse transcriptase reaction was oligodT which was provided in the kit. The gene specific primer (5'-CACATCCCTCATTATAGTCAGAAAG-3'; SEQ ID NO: 149) annealed to nucleotides 738-762 in the 2 kb contig (SEQ ID NO: 148) and was used with the internal primer in the kit to perform the nested PCR. The RACE procedure was done as described in the manual provided with the kit. Nested PCR products were cloned into a TA Topo vector (Invitrogen) and analyzed by restriction enzyme (RE) digestion. Based on the sequence of the contig, a restriction enzyme map was constructed and

prospective clones were digested with SpeI and NsiI separately. From these data it appeared that only the RACE reactions from the placental mRNA yielded the predicted clones. Clones with the predictive RE pattern were sequenced (Retrogen Inc.). The sequencing data revealed that the clones all overlapped with the 2 kb contig and actually
5 extended the contig about 300 nucleotides at the 5' end, thus yielding a new contig of about 2.3 kb (SEQ ID NO: 150). Because the full-length gene, predicted to be about 7 to about 7.5 kb in length (see Example 5 above) was not yet obtained, it was necessary to "walk down" the length of the mRNA to clone this gene.

10 The 2.3 kb contig (SEQ ID NO: 150) was then used as the query sequence for a BLAST search to see if the contig could be extended further. This search yielded the EST fragment hv79F02 (GenBank Accession No. BE327693) (SEQ ID NO: 151) which overlapped the 2.3 kb contig and extended the sequence about 300 more bases at the 5' end yielding a contig of about 2.6 kb (SEQ ID NO: 152). This contig was then
15 used as the query sequence to search the human genome sequence at NCBI. The results of this search indicated that the contig hybridized with greater than 98% identity to a region tentatively assigned to chromosome 1.

A series of 10 primers were then designed based on the sequence about
20 3-5 kb upstream of the 5' end of where the 2.6 kb contig hybridized on chromosome 1. These primers were utilized along with contig specific primers in PCR reactions of a RACE ready cDNA preparation of placental mRNA (Ambion). The PCR reactions from two of these primers (5'-TAACAATCCTTTGGAAGTCACTACTGG-3'; SEQ ID NO: 153; and 5'-AAGCCCAGCATTGCTAAGAGG-3'; SEQ ID NO: 154) gave products of
25 predicted size and were subcloned into TA-TOPO vectors (Invitrogen) and sequenced. The sequencing data showed that these PCR products were overlapping with the sequence of the 2.6 kb contig and extended the contig at the 5' end by about 800 bp, resulting in a gene fragment of a total of about 3.4 kb (SEQ ID NO: 155).

The 3.4 kb contig (SEQ ID NO: 155) was then used as the query sequence to search the proprietary transcript database of the Celera Genomics Group. This produced a hit with Celera transcript hCT 1782960 (SEQ ID NO: 156), which overlaps significantly with the 5' region of the 3.4 kb contig (SEQ ID NO: 155) and extends the
5 contig about 750 bp at the 5' end, yielding a new contig of a total of about 4.1 kb (SEQ ID NO: 157).

To determine if the 750 bp described above indeed extended the gene, PCR experiments were undertaken using this 750 bp region of the 4.1 kb contig (SEQ ID
10 NO: 157) as the template for primer design. When these primers (SEQ ID NOS: 159 and 160) were used in combination with contig specific primers (SEQ ID NOS: 161, 162 and 163), PCR products of the expected sizes were obtained. Sequencing confirmed that these PCR products were overlapping with the 3.4 kb contig (SEQ ID NO: 155) and that the new 750 bp at the 5' end indeed extended the contig to about 4.1 kb.

15

The sequence of the 4.1 kb contig (SEQ ID NO: 157) contains an open reading frame (nucleotides 3 – 962) whose encoded protein (SEQ ID NO: 158) has significant identity with the hypothetical protein KIAA0456 (GENBANK Acession No: AB007925) (SEQ ID NO: 165), which is believed to be a GTPase activating protein.
20 This suggests that the gene, which is shown herein to be involved in conferring resistance to Fas-induced apoptosis, may encode a GTPase activating protein.

The inability to find an mRNA of about 7 kb in the placental cDNA prompted the performance of a new Northern blot on mRNA from colon, brain and
25 placental tissues, utilizing the same probe described above in Example 5. The results indicated that the gene containing EST2 had different sized mRNAs depending on the tissue in which it was expressed. The colon tissue contained an mRNA of about 7 kb; placenta had an mRNA of about 4.5kb; and brain contained two species of the mRNA -- a predominate band of about 5.5 kb and a minor band of about 7 kb. Thus, the RACE

and contig assembly efforts described above were consistent with the size of the message present in placenta.

To determine whether the assembled contig represented a true messenger RNA, a lambda phage brain cDNA library (Human Brain Large-Insert cDNA Library, Clontech) was screened. This library was chosen because it contained both an approximately 5.5 kb mRNA and an approximately 7kb mRNA, the latter being consistent with the size of the message present in colon tissue. The probe for these studies was a 500 bp NsiI fragment present in the 3' end of the contig and lies about 50 bases upstream of the probe used for the Northern blots. From the chosen brain library, the 5.5 kb species of the mRNA was readily obtained and sequenced (SEQ ID NO: 166). This sequence of the 5.5 kb cDNA from the brain library contains the complete sequence of the 4.1 kb contig (SEQ ID NO: 157) and extends it at both the 5' and 3' ends of the sequence. The sequence that extends the 5' end of the gene also extends the open reading frame that was present in the 4.1 kb contig (SEQ ID NO: 157), with further sequence identity to the GTPase protein described above. This further confirmed the identity of the protein product for this gene as a potential GTPase activating protein.

Example 6: In vitro efficacy

This example shows that ribozymes can treat cancer cells by making them more susceptible to apoptosis and more likely to respond to treatment.

Specifically, a bladder cancer cell line resistant to Fas was selected (regarding the role of Fas/Fas ligand system, including its role in cancer, see, for example, Gruss *et al.*, J. Exp. Med.; 181:1235-38 (1995); Kagi *et al.*, Science, 265:528-530 (1994); Nagata *et al.*, Cell, 88:355-65 (1997); Runic, J. Clin. Endocrinol. Metab., 81:3119-22 (1996); Suda *et al.*, Cell, 75:1169-78 (1993); and Perabo *et al.*, Urology Oncology, 6:163-69 (2001)). These cells were transfected with one or both of the following ribozyme substrate binding sequences: 1) Tv2-2 (EST2-2 (SEQ ID NO: 97);

and b) Sr6 (RAP6 (SEQ ID NO: 19). These binding sequences were each part of a synthetic, chimeric DNA/RNA hammerhead ribozyme structure (SEQ ID NOS: 6 and 5, respectively) that was used for the transfection. The specific cell line used was TCCSUP, which was derived from an anaplastic transitional cell carcinoma (TCC) in the neck of the urinary bladder of a 67 years old female.

These cells were transfected with either 1) Tv2-2; 2) SR6; 3) a “scrambled” control (identical structure to Tv2-2 or SR6 but with an additional non-specific sequence that cannot bind to any known gene); or 4) a combination of Tv2-2 and SR6 at a ratio of 1:1.

Cells were transfected accordingly to the manufacturer recommendations (GTS, CA – USA). In brief, cells were plated and 24 hours later, transfected using a Gene Porter kit with the different ribozymes. After 24 additional hours, cells were treated with Fas antibody. Eighteen hours later, cells were analyzed with Annexin V detection method. The results of these experiments are presented in Figure 8.

As shown in Figure 8, the presence of each ribozyme having the indicated substrate binding sequence, combined with Fas, dramatically increased the percentage of cells that underwent apoptosis, as compared to the presence of these ribozymes without Fas. Moreover, the combination of both ribozymes with Fas more than doubled the percentage of cell undergoing apoptosis. Thus, this example demonstrates that Tv2-2 and SR6 were able to lift the cell resistance to Fas and therefore make them susceptible to apoptosis and, accordingly, more likely to respond to treatment.

All references made herein, including journal articles, patent applications, patents and other publications, are incorporated by reference in their entirety.

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<110> Immusol Incorporated
 Tritz, Richard
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 Habita, Cellia
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<400> 30

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<213> Homo sapiens

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<210> 32

<211> 953

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17/90

<212> DNA

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<308> GenBank BG116747

<309> 2001-01-29

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<212> DNA

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<309> 2001-01-29

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gagaatcgca ttccttgagg aaagagcagc atgtgggaaa acataaatgc acgcaataac 240
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 ctggctctgc tggactgggt agatataaca ctatttaa at gacccaatct cattacatgt 420
 gaagatttcc attttttagg ttacgtaaga aatttggacc taaaaatctt gcattttaag 480
 acagtcttgt cagaattact tttggctcta aatgaattct gtaacatttg tattctaaat 540
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 tcatatatat ctaagcagtt ataatagggt gatttttgta atttaaaaaa tgtaaaaatg 180
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 ttcattatct aaggagtgtg ttgaacactc tctagaggct ttttaataata ggattgttta 480
 gctggctctgt ctggactggg tagatataac actattttaa tgacccaatc tcattacatt 540
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tttaagacag ctctttgtca agaattactt tttggctcta aatgaattcc tgtaacattt 660
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 ctgccaccct tcactatctg gcttcacatcat ggtgtcctct acccatccct gcttgtgggt 780
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 tcgcggtgca ccatggacgg tcagcgccag ataacaaaag ggggggcaac acacgcaggc 840

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20/90

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857

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 aaattttgga cctaaaaatc ttgcatttta agacagtctt tgtcagaatt actttttggc 480
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PCT/US02/15198

51/90

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<213> Artificial

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53/90

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2377

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gtgtcactgc actccagcct gggtgacaga gtaagactct gcctaaaaaa aaaaaaaaaa 3300
aaa 3303

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<210> 156

<211> 935

<212> DNA

<213> Homo sapiens

<400> 156

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actcggtcac gaagacatat cacatgtaca atgccgacag catcagtgct cagagcaaac 120

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```

taaaggaggc ggagaagcag gaggagaagc aaattggtaa atcggtaaag caggaggacc 180

```

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ggcagacccc acgctcccct gactccacgg ccaacgttcg cattgaggag aaacatgtcc 240
ggaggagctc agtgaagaag attgagaaga tgaaggagaa gcgccaagcc aagtacacgg 300
agaataagct gaaggccatc aaagcccgga atgagtactt gctggctttg gaggcaacca 360
atgcatctgt cttcaagtac tacatccatg acctatctga ctttattgat cagtgttgtg 420
acttaggcta ccatgcaagt ctgaaccggg ctctacgcac cttcctctct gctgagttaa 480
acctggaaca gtcgaagcat gagggctctg atgccatcga gaatgcagta gaaaacctgg 540
atgccaccag tgacaagcag cgcctcatgg agatgtacaa caacgtcttc tgcccccta 600
tgaagtttga gtttcagccc cacatggggg atatggcttc ccagctctgt gccagcagc 660
ctgtccagag tgagctggta cagagatgcc aacaactgca gtctcgctta tccactctaa 720
agattgaaaa cgaagaggta aagaagacaa tggaggccac cctgcaaacc atccaggaca 780
ttgtgactgt cgaggacttc gatgtgtctg actgcttcca gtacagcaac tccatggagt 840
ccgtcaagtc cacggtctct gaaaccttca tgagcaagcc cagcattgct aagaggagag 900
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<210> 157
<211> 4171
<212> DNA
<213> Artificial

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<220>
<223> Contig

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<220>
<221> CDS
<222> (3)..(962)
<223>

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<400> 157
tg cag agt aaa gaa gtc ggc cag cag ctc caa gat gat ttg atg aag 47
  Gln Ser Lys Glu Val Gly Gln Gln Leu Gln Asp Asp Leu Met Lys
    1             5             10             15

gtc ctg aac gag ctc tac tcg gtc atg aag aca tat cac atg tac aat 95
Val Leu Asn Glu Leu Tyr Ser Val Met Lys Thr Tyr His Met Tyr Asn
          20             25             30

gcc gac agc atc agt gct cag agc aaa cta aag gag gcg gag aag cag 143
Ala Asp Ser Ile Ser Ala Gln Ser Lys Leu Lys Glu Ala Glu Lys Gln
          35             40             45

gag gag aag caa att ggt aaa tcg gta aag cag gag gac cgg cag acc 191
Glu Glu Lys Gln Ile Gly Lys Ser Val Lys Gln Glu Asp Arg Gln Thr
          50             55             60

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cca	cgc	tcc	cct	gac	tcc	acg	gcc	aac	gtt	cgc	att	gag	gag	aaa	cat	239
Pro	Arg	Ser	Pro	Asp	Ser	Thr	Ala	Asn	Val	Arg	Ile	Glu	Glu	Lys	His	
	65					70					75					
gtc	cgg	agg	agc	tca	gtg	aag	aag	att	gag	aag	atg	aag	gag	aag	cgc	287
Val	Arg	Arg	Ser	Ser	Val	Lys	Lys	Ile	Glu	Lys	Met	Lys	Glu	Lys	Arg	
	80					85				90					95	
caa	gcc	aag	tac	acg	gag	aat	aag	ctg	aag	gcc	atc	aaa	gcc	cgg	aat	335
Gln	Ala	Lys	Tyr	Thr	Glu	Asn	Lys	Leu	Lys	Ala	Ile	Lys	Ala	Arg	Asn	
				100				105						110		
gag	tac	ttg	ctg	gct	ttg	gag	gca	acc	aat	gca	tct	gtc	ttc	aag	tac	383
Glu	Tyr	Leu	Leu	Ala	Leu	Glu	Ala	Thr	Asn	Ala	Ser	Val	Phe	Lys	Tyr	
			115					120					125			
tac	atc	cat	gac	cta	tct	gac	ctt	att	gat	cag	tgt	tgt	gac	tta	ggc	431
Tyr	Ile	His	Asp	Leu	Ser	Asp	Leu	Ile	Asp	Gln	Cys	Cys	Asp	Leu	Gly	
		130					135					140				
tac	cat	gca	agt	ctg	aac	cgg	gct	cta	cgc	acc	ttc	ctc	tct	gct	gag	479
Tyr	His	Ala	Ser	Leu	Asn	Arg	Ala	Leu	Arg	Thr	Phe	Leu	Ser	Ala	Glu	
	145					150					155					
tta	aac	ctg	gaa	cag	tcg	aag	cat	gag	ggc	ctg	gat	gcc	atc	gag	aat	527
Leu	Asn	Leu	Glu	Gln	Ser	Lys	His	Glu	Gly	Leu	Asp	Ala	Ile	Glu	Asn	
	160				165				170						175	
gca	gta	gaa	aac	ctg	gat	gcc	acc	agt	gac	aag	cag	cgc	ctc	atg	gag	575
Ala	Val	Glu	Asn	Leu	Asp	Ala	Thr	Ser	Asp	Lys	Gln	Arg	Leu	Met	Glu	
				180					185					190		
atg	tac	aac	aac	gtc	ttc	tgc	ccc	cct	atg	aag	ttt	gag	ttt	cag	ccc	623
Met	Tyr	Asn	Asn	Val	Phe	Cys	Pro	Pro	Met	Lys	Phe	Glu	Phe	Gln	Pro	
			195					200					205			
cac	atg	ggg	gat	atg	gct	tcc	cag	ctc	tgt	gcc	cag	cag	cct	gtc	cag	671
His	Met	Gly	Asp	Met	Ala	Ser	Gln	Leu	Cys	Ala	Gln	Gln	Pro	Val	Gln	
		210					215					220				
agt	gag	ctg	gta	cag	aga	tgc	caa	caa	ctg	cag	tct	cgc	tta	tcc	act	719
Ser	Glu	Leu	Val	Gln	Arg	Cys	Gln	Gln	Leu	Gln	Ser	Arg	Leu	Ser	Thr	
	225					230					235					
cta	aag	att	gaa	aac	gaa	gag	gta	aag	aag	aca	atg	gag	gcc	acc	ctg	767
Leu	Lys	Ile	Glu	Asn	Glu	Glu	Val	Lys	Lys	Thr	Met	Glu	Ala	Thr	Leu	
	240				245					250					255	
caa	acc	atc	cag	gac	att	gtg	act	gtc	gag	gac	ttc	gat	gtg	tct	gac	815
Gln	Thr	Ile	Gln	Asp	Ile	Val	Thr	Val	Glu	Asp	Phe	Asp	Val	Ser	Asp	
				260					265					270		
tgc	ttc	cag	tac	agc	aac	tcc	atg	gag	tcc	gtc	aag	tcc	acg	gtc	tct	863
Cys	Phe	Gln	Tyr	Ser	Asn	Ser	Met	Glu	Ser	Val	Lys	Ser	Thr	Val	Ser	
			275					280					285			

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60/90

gaa acc ttc atg agc aag ccc agc att gct aag agg aga gcc aac cag	911
Glu Thr Phe Met Ser Lys Pro Ser Ile Ala Lys Arg Arg Ala Asn Gln	
290 295 300	
caa gag aca gag cag ttt tat ttc aca gta agg gag tgc tat ggc ttt	959
Gln Glu Thr Glu Gln Phe Tyr Phe Thr Val Arg Glu Cys Tyr Gly Phe	
305 310 315	
taa agagcgtcag catgcactgc agcactcaag ggagatttgg aactcagagt	1012
ccttgттаag tgtctgaagg acaggcgttg aatatcttag atacgaatgt gggcatactc	1072
agagaccatc cctacagtta aagggtgcaaa cattaaaagt tgtatatgtc taacagggat	1132
ccgccaaga gaaaggatgc tccaagtat acaactaaga agattttctt ttttaagaaa	1192
tttttaacta gctagtaggc tttcactgga aagtttcctt ctcaggcaca ggggatcctg	1252
aaaggggaac ttcactcttt agttcttgga gagtacatac aaatattcat aataacacat	1312
attttgttta taaaaatcta taatctcttc taggtgatat gatgacatta ttttataact	1372
tttattgttg ggaaactatt ttttctaatt attgctaaaa cttaaaggat gggtaatatg	1432
cagcattact attttgcaca taattccaaa acatcgtatt ttcttattca tgtatctcta	1492
gtcttctttt agacagttgg accctttttt ctcttttttt tttttttttt ttttttttaa	1552
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ttctgatgac caagaaagga aaaattaagt ttgcagatgt gagatgaaat atagccagtg	1732
aatatgcata ctgattctga atgaaaggaa ttaacttttc agtcaagaaa cagtctgcat	1792
gcggggtaaa ttgaattttt cctgcaactg gaatgatttg ttttaattctt ctttgaacac	1852
tgccctttct ccagtaagaa cactaatgat ttgctaatat tttttaaaga aatctgtttt	1912
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gaatgatata tcagtactat tcttctaaaa caacttttta aaaatgatta taciaagcca	2032
aatatgctca ttatataaaa tttagaagca aaaagaagga aataaaaatt ttccataatt	2092
ctaccagcta gagataatgg tgttagaata tattcctttc taatctgttt tctatgcatg	2152
cacaaacaca tatgtgagca catatttata attttattct aaaaaatagg atactgctgt	2212
acatattggt ttacaatcta agtcatataa ttataatatt ctttaaacad atttatgagt	2272
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cctgtaatcc cagcgtgtgt ggagcctgag gcgggtgggt ctcttgaggc caggagttca 3952
agaccagcct ggacaacatg gtgaaaccct gtctctacta aaaacacaaa aattagctga 4012
gtgtgggtggc aggcgcctgt aatcccagct actcaggagg ctaagggtggg aggattactt 4072
gaaccgggga ggcatagggt gtagtgagcc aagatcgtgt cactgcactc cagcctgggt 4132

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gacagagtaa gactctgcct aaaaaaaaaa aaaaaaaaaa

4171

<210> 158
 <211> 319
 <212> PRT
 <213> Artificial

<220>
 <223> Contig

<400> 158

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Leu Asn Glu Leu Tyr Ser Val Met Lys Thr Tyr His Met Tyr Asn Ala
 20 25 30

Asp Ser Ile Ser Ala Gln Ser Lys Leu Lys Glu Ala Glu Lys Gln Glu
 35 40 45

Glu Lys Gln Ile Gly Lys Ser Val Lys Gln Glu Asp Arg Gln Thr Pro
 50 55 60

Arg Ser Pro Asp Ser Thr Ala Asn Val Arg Ile Glu Glu Lys His Val
 65 70 75 80

Arg Arg Ser Ser Val Lys Lys Ile Glu Lys Met Lys Glu Lys Arg Gln
 85 90 95

Ala Lys Tyr Thr Glu Asn Lys Leu Lys Ala Ile Lys Ala Arg Asn Glu
 100 105 110

Tyr Leu Leu Ala Leu Glu Ala Thr Asn Ala Ser Val Phe Lys Tyr Tyr
 115 120 125

Ile His Asp Leu Ser Asp Leu Ile Asp Gln Cys Cys Asp Leu Gly Tyr
 130 135 140

His Ala Ser Leu Asn Arg Ala Leu Arg Thr Phe Leu Ser Ala Glu Leu
 145 150 155 160

Asn Leu Glu Gln Ser Lys His Glu Gly Leu Asp Ala Ile Glu Asn Ala
 165 170 175

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Val Glu Asn Leu Asp Ala Thr Ser Asp Lys Gln Arg Leu Met Glu Met
 180 185 190

Tyr Asn Asn Val Phe Cys Pro Pro Met Lys Phe Glu Phe Gln Pro His
 195 200 205

Met Gly Asp Met Ala Ser Gln Leu Cys Ala Gln Gln Pro Val Gln Ser
 210 215 220

Glu Leu Val Gln Arg Cys Gln Gln Leu Gln Ser Arg Leu Ser Thr Leu
 225 230 235 240

Lys Ile Glu Asn Glu Glu Val Lys Lys Thr Met Glu Ala Thr Leu Gln
 245 250 255

Thr Ile Gln Asp Ile Val Thr Val Glu Asp Phe Asp Val Ser Asp Cys
 260 265 270

Phe Gln Tyr Ser Asn Ser Met Glu Ser Val Lys Ser Thr Val Ser Glu
 275 280 285

Thr Phe Met Ser Lys Pro Ser Ile Ala Lys Arg Arg Ala Asn Gln Gln
 290 295 300

Glu Thr Glu Gln Phe Tyr Phe Thr Val Arg Glu Cys Tyr Gly Phe
 305 310 315

<210> 159
 <211> 27
 <212> DNA
 <213> Artificial

<220>
 <223> Primer

<400> 159
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27

<210> 160
 <211> 26
 <212> DNA
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<220>
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<400> 160

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64/90

gagaggtatg attggtggta ggatga

26

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<220>
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<400> 161
cttcatcaaa tcattcttgga gctgctg

27

<210> 162
<211> 25
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<220>
<223> Primer

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gtaatgctgc atattaccca tcctt

25

<210> 163
<211> 26
<212> DNA
<213> Artificial

<220>
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<400> 163
tgcttctccg cctccttttag tttgct

26

<210> 164
<211> 6305
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(3288)
<223> Hypothetical protein

<300>
<308> GenBank AB007925
<309> 1998-08-13

<400> 164
cgg acg cgt ggg ttg gat ttt ttc cgt gga tct atc aat tca caa ttc
Arg Thr Arg Gly Leu Asp Phe Phe Arg Gly Ser Ile Asn Ser Gln Phe

48

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65/90

1	5				10				15								
gaa ttt gga aga aag aag gaa aac atg acg tct cca gcc aaa ttc aaa	Glu Phe Gly Arg Lys Lys Glu Asn Met Thr Ser Pro Ala Lys Phe Lys				20 25 30												96
aag gat aag gag atc ata gca gag tac gat act cag gtc aaa gag atc	Lys Asp Lys Glu Ile Ile Ala Glu Tyr Asp Thr Gln Val Lys Glu Ile				35 40 45												144
cgt gct cag ctc aca gag cag atg aaa tgc ctg gac cag cag tgt gag	Arg Ala Gln Leu Thr Glu Gln Met Lys Cys Leu Asp Gln Gln Cys Glu				50 55 60												192
ctt cgg gtg caa ctg ttg cag gac ctc cag gac ttc ttc cga aag aag	Leu Arg Val Gln Leu Leu Gln Asp Leu Gln Asp Phe Phe Arg Lys Lys				65 70 75 80												240
gca gag att gag atg gac tac tcc cgc aac ctg gag aag ctg gca gaa	Ala Glu Ile Glu Met Asp Tyr Ser Arg Asn Leu Glu Lys Leu Ala Glu				85 90 95												288
cgc ttc ctg gcc aag aca cgc agc acc aag gac cag caa ttc aag aag	Arg Phe Leu Ala Lys Thr Arg Ser Thr Lys Asp Gln Gln Phe Lys Lys				100 105 110												336
gat cag aat gtt ctc tct cca gtc aac tgc tgg aat ctc ctc tta aac	Asp Gln Asn Val Leu Ser Pro Val Asn Cys Trp Asn Leu Leu Leu Asn				115 120 125												384
cag gtg aag cgg gaa agc agg gac cat acc acc ctg agt gac atc tac	Gln Val Lys Arg Glu Ser Arg Asp His Thr Thr Leu Ser Asp Ile Tyr				130 135 140												432
ctg aat aat atc att cct cga ttt gta caa gtc agc gag gac tca gga	Leu Asn Asn Ile Ile Pro Arg Phe Val Gln Val Ser Glu Asp Ser Gly				145 150 155 160												480
aga ctc ttt aaa aag agt aaa gaa gtc ggc cag cag ctc caa gat gat	Arg Leu Phe Lys Lys Ser Lys Glu Val Gly Gln Gln Leu Gln Asp Asp				165 170 175												528
ttg atg aag gtc ctg aac gag ctc tac tcg gtg atg aag aca tat cac	Leu Met Lys Val Leu Asn Glu Leu Tyr Ser Val Met Lys Thr Tyr His				180 185 190												576
atg tac aat gcc gac agc atc agt gct cag agc aaa cta aag gag gcg	Met Tyr Asn Ala Asp Ser Ile Ser Ala Gln Ser Lys Leu Lys Glu Ala				195 200 205												624
gag aag cag gag gag aag caa att ggt aaa tcg gta aag cag gag gac	Glu Lys Gln Glu Glu Lys Gln Ile Gly Lys Ser Val Lys Gln Glu Asp				210 215 220												672
cgg cag acc cca cgc tcc cct gac tcc acg gcc aac gtt cgc att gag	Arg Gln Thr Pro Arg Ser Pro Asp Ser Thr Ala Asn Val Arg Ile Glu				225 230 235 240												720

gag	aaa	cat	gtc	cgg	agg	agc	tca	gtg	aag	aag	att	gag	aag	atg	aag	768
Glu	Lys	His	Val	Arg	Arg	Ser	Ser	Val	Lys	Lys	Ile	Glu	Lys	Met	Lys	
				245					250					255		
gag	aag	cgt	caa	gcc	aag	tac	acg	gag	aat	aag	ctg	aag	gcc	atc	aaa	816
Glu	Lys	Arg	Gln	Ala	Lys	Tyr	Thr	Glu	Asn	Lys	Leu	Lys	Ala	Ile	Lys	
			260					265					270			
gcc	cgg	aat	gag	tac	ttg	ctg	gct	ttg	gag	gca	acc	aat	gca	tct	gtc	864
Ala	Arg	Asn	Glu	Tyr	Leu	Leu	Ala	Leu	Glu	Ala	Thr	Asn	Ala	Ser	Val	
		275					280					285				
ttc	aag	tac	tac	atc	cat	gac	cta	tct	gac	ctt	att	gat	cag	tgt	tgt	912
Phe	Lys	Tyr	Tyr	Ile	His	Asp	Leu	Ser	Asp	Leu	Ile	Asp	Gln	Cys	Cys	
	290					295					300					
gac	tta	ggc	tac	cat	gca	agt	ctg	aac	cgg	gct	cta	cgc	acc	ttc	ctc	960
Asp	Leu	Gly	Tyr	His	Ala	Ser	Leu	Asn	Arg	Ala	Leu	Arg	Thr	Phe	Leu	
305					310				315						320	
tct	gct	gag	tta	aac	ctg	gaa	cag	tcg	aag	cat	gag	ggc	ctg	gat	gcc	1008
Ser	Ala	Glu	Leu	Asn	Leu	Glu	Gln	Ser	Lys	His	Glu	Gly	Leu	Asp	Ala	
				325					330					335		
atc	gag	aat	gca	gta	gaa	aac	ctg	gat	gcc	acc	agt	gac	aag	cag	cgc	1056
Ile	Glu	Asn	Ala	Val	Glu	Asn	Leu	Asp	Ala	Thr	Ser	Asp	Lys	Gln	Arg	
			340					345					350			
ctc	atg	gag	atg	tac	aac	aac	gtc	ttc	tgc	ccc	cct	atg	aag	ttt	gag	1104
Leu	Met	Glu	Met	Tyr	Asn	Asn	Val	Phe	Cys	Pro	Pro	Met	Lys	Phe	Glu	
		355					360					365				
ttt	cag	ccc	cac	atg	ggg	gat	atg	gct	tcc	cag	ctc	tgt	gcc	cag	cag	1152
Phe	Gln	Pro	His	Met	Gly	Asp	Met	Ala	Ser	Gln	Leu	Cys	Ala	Gln	Gln	
	370					375					380					
cct	gtc	cag	agt	gag	ctg	gta	cag	aga	tgc	caa	caa	ctg	cag	tct	cgc	1200
Pro	Val	Gln	Ser	Glu	Leu	Val	Gln	Arg	Cys	Gln	Gln	Leu	Gln	Ser	Arg	
385					390					395					400	
tta	tcc	act	cta	aag	att	gaa	aac	gaa	gag	gta	aag	aag	aca	atg	gag	1248
Leu	Ser	Thr	Leu	Lys	Ile	Glu	Asn	Glu	Glu	Val	Lys	Lys	Thr	Met	Glu	
				405				410						415		
gcc	acc	ctg	caa	acc	atc	cag	gac	att	gtg	act	gtc	gag	gac	ttt	gat	1296
Ala	Thr	Leu	Gln	Thr	Ile	Gln	Asp	Ile	Val	Thr	Val	Glu	Asp	Phe	Asp	
			420					425					430			
gtg	tct	gac	tgc	ttc	cag	tac	agc	aac	tcc	atg	gag	tcc	gtc	aag	tcc	1344
Val	Ser	Asp	Cys	Phe	Gln	Tyr	Ser	Asn	Ser	Met	Glu	Ser	Val	Lys	Ser	
		435					440					445				
acg	gtc	tct	gaa	acc	ttc	atg	agc	aag	ccc	agc	att	gct	aag	agg	aga	1392
Thr	Val	Ser	Glu	Thr	Phe	Met	Ser	Lys	Pro	Ser	Ile	Ala	Lys	Arg	Arg	
	450					455					460					

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gcc aac cag caa gag aca gag cag ttt tat ttc aca aaa atg aaa gag	1440
Ala Asn Gln Gln Glu Thr Glu Gln Phe Tyr Phe Thr Lys Met Lys Glu	
465 470 475 480	
tac ctg gag ggc agg aac ctc atc acc aag tta caa gcc aag cat gac	1488
Tyr Leu Glu Gly Arg Asn Leu Ile Thr Lys Leu Gln Ala Lys His Asp	
485 490 495	
ctt ctg cag aaa acc ctg gga gaa agt cag cgg aca gat tgc agt cta	1536
Leu Leu Gln Lys Thr Leu Gly Glu Ser Gln Arg Thr Asp Cys Ser Leu	
500 505 510	
gcc agg cgc agc tca act gtg agg aaa cag gac tcc agc cag gca att	1584
Ala Arg Arg Ser Ser Thr Val Arg Lys Gln Asp Ser Ser Gln Ala Ile	
515 520 525	
cct ctg gtg gtg gaa agc tgt atc cgg ttt atc agc aga cac gga cta	1632
Pro Leu Val Val Glu Ser Cys Ile Arg Phe Ile Ser Arg His Gly Leu	
530 535 540	
cag cat gaa gga att ttc cgg gtg tca gga tcc cag gtg gaa gtg aat	1680
Gln His Glu Gly Ile Phe Arg Val Ser Gly Ser Gln Val Glu Val Asn	
545 550 555 560	
gac atc aaa aat gcc ttt gag aga gga gag gac ccc ctg gct ggg gac	1728
Asp Ile Lys Asn Ala Phe Glu Arg Gly Glu Asp Pro Leu Ala Gly Asp	
565 570 575	
cag aac gac cat gac atg gat tcc ata gct ggt gtc ctg aag ctt tac	1776
Gln Asn Asp His Asp Met Asp Ser Ile Ala Gly Val Leu Lys Leu Tyr	
580 585 590	
ttc cgg ggg ctg gaa cac cct ctc ttc ccc aag gac atc ttt cat gac	1824
Phe Arg Gly Leu Glu His Pro Leu Phe Pro Lys Asp Ile Phe His Asp	
595 600 605	
ctg atg gcc tgc gtc aca atg gac aac ctg cag gag aga gct ctg cac	1872
Leu Met Ala Cys Val Thr Met Asp Asn Leu Gln Glu Arg Ala Leu His	
610 615 620	
atc cgg aaa gtc ctc cta gtc ctg ccc aaa acc act ctg att atc atg	1920
Ile Arg Lys Val Leu Leu Val Leu Pro Lys Thr Thr Leu Ile Ile Met	
625 630 635 640	
aga tac ctc ttt gcc ttc ctc aat cat tta tca cag ttc agt gaa gag	1968
Arg Tyr Leu Phe Ala Phe Leu Asn His Leu Ser Gln Phe Ser Glu Glu	
645 650 655	
aac atg atg gac ccc tac aac ctc gcc atc tgc ttc ggg ccc tcg cta	2016
Asn Met Met Asp Pro Tyr Asn Leu Ala Ile Cys Phe Gly Pro Ser Leu	
660 665 670	
atg tca gtg cca gag ggc cac gac cag gtg tcc tgc caa gcc cac gtg	2064
Met Ser Val Pro Glu Gly His Asp Gln Val Ser Cys Gln Ala His Val	
675 680 685	
aat gag ctg atc aaa acc atc atc atc cag cat gag aac atc ttc cca	2112

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Asn	Glu	Leu	Ile	Lys	Thr	Ile	Ile	Ile	Gln	His	Glu	Asn	Ile	Phe	Pro	
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agc	ccc	agg	gag	ctg	gag	ggc	cct	gtc	tac	agc	aga	gga	gga	agc	atg	2160
Ser	Pro	Arg	Glu	Leu	Glu	Gly	Pro	Val	Tyr	Ser	Arg	Gly	Gly	Ser	Met	
705					710					715					720	
gag	gat	tac	tgt	gat	agc	cct	cat	gga	gag	act	acc	ccg	gtt	gaa	gac	2208
Glu	Asp	Tyr	Cys	Asp	Ser	Pro	His	Gly	Glu	Thr	Thr	Pro	Val	Glu	Asp	
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tca	acc	cag	gat	gtg	acc	gca	gag	cac	cac	acg	agc	gat	gac	gaa	tgt	2256
Ser	Thr	Gln	Asp	Val	Thr	Ala	Glu	His	His	Thr	Ser	Asp	Asp	Glu	Cys	
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gag	ccc	atc	gag	gcc	att	gcc	aag	ttt	gac	tac	gtg	ggc	cgg	aca	gcc	2304
Glu	Pro	Ile	Glu	Ala	Ile	Ala	Lys	Phe	Asp	Tyr	Val	Gly	Arg	Thr	Ala	
		755					760					765				
cga	gag	ctg	tcc	ttt	aag	aag	gga	gca	tcc	ctg	ctg	ctt	tac	cag	cgg	2352
Arg	Glu	Leu	Ser	Phe	Lys	Lys	Gly	Ala	Ser	Leu	Leu	Leu	Tyr	Gln	Arg	
	770					775					780					
gct	tcc	gac	gac	tgg	tgg	gaa	ggc	cgg	cac	aat	ggc	atc	gac	gga	ctc	2400
Ala	Ser	Asp	Asp	Trp	Trp	Glu	Gly	Arg	His	Asn	Gly	Ile	Asp	Gly	Leu	
785					790					795					800	
atc	ccc	cat	cag	tac	atc	gtg	gtc	caa	gac	acc	gag	gac	ggg	gtc	gtg	2448
Ile	Pro	His	Gln	Tyr	Ile	Val	Val	Gln	Asp	Thr	Glu	Asp	Gly	Val	Val	
				805					810					815		
gag	agg	tcc	agc	ccc	aag	tct	gag	att	gag	gtc	att	tct	gag	cca	cct	2496
Glu	Arg	Ser	Ser	Pro	Lys	Ser	Glu	Ile	Glu	Val	Ile	Ser	Glu	Pro	Pro	
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gaa	gaa	aag	gtg	aca	gcc	aga	gcg	ggg	gcc	agc	tgt	ccc	agt	ggg	ggg	2544
Glu	Glu	Lys	Val	Thr	Ala	Arg	Ala	Gly	Ala	Ser	Cys	Pro	Ser	Gly	Gly	
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cat	gta	gcc	gat	att	tat	ctt	gca	aac	atc	aac	aag	caa	agg	aag	cgt	2592
His	Val	Ala	Asp	Ile	Tyr	Leu	Ala	Asn	Ile	Asn	Lys	Gln	Arg	Lys	Arg	
	850					855					860					
cca	gaa	tct	ggg	agc	atc	cgg	aaa	act	ttt	cgg	agt	gac	agc	cat	ggg	2640
Pro	Glu	Ser	Gly	Ser	Ile	Arg	Lys	Thr	Phe	Arg	Ser	Asp	Ser	His	Gly	
865					870					875					880	
ctg	agc	agt	tcc	ctg	act	gac	tcc	tcc	tcc	cca	ggg	gtg	ggg	gct	agc	2688
Leu	Ser	Ser	Ser	Leu	Thr	Asp	Ser	Ser	Ser	Pro	Gly	Val	Gly	Ala	Ser	
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tgc	cgc	cca	tcc	tcc	cag	ccc	atc	atg	agc	cag	agc	ctc	ccc	aaa	gaa	2736
Cys	Arg	Pro	Ser	Ser	Gln	Pro	Ile	Met	Ser	Gln	Ser	Leu	Pro	Lys	Glu	
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Gly	Pro	Asp	Lys	Cys	Ser	Ile	Ser	Gly	His	Gly	Ser	Leu	Asn	Ser	Ile	

915	920	925	
agc cgc cac tca tcc ctg aag aat cgg ctg gat agt cca cag atc cgg			2832
Ser Arg His Ser Ser Leu Lys Asn Arg Leu Asp Ser Pro Gln Ile Arg			
930	935	940	
aag act gcc aca gcg gga agg tca aaa agc ttc aat aac cat cgg ccc			2880
Lys Thr Ala Thr Ala Gly Arg Ser Lys Ser Phe Asn Asn His Arg Pro			
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atg gac cct gag gtc att gct cag gat att gag gca aca atg aac tcg			2928
Met Asp Pro Glu Val Ile Ala Gln Asp Ile Glu Ala Thr Met Asn Ser			
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gcc ctg aat gag cta cgg gaa cta gaa cgg cag agc agt gtc aaa cac			2976
Ala Leu Asn Glu Leu Arg Glu Leu Glu Arg Gln Ser Ser Val Lys His			
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Thr Pro Asp Val Val Leu Asp Thr Leu Glu Pro Leu Lys Thr Ser Pro			
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gtg gtg gcc ccc acg tca gag ccc tcc agc cct ctg cac acc cag			3069
Val Val Ala Pro Thr Ser Glu Pro Ser Ser Pro Leu His Thr Gln			
	1010	1015	1020
ctc ctc aag gac ccc gag ccc gcc ttc cag cgc agc gcc agt act			3114
Leu Leu Lys Asp Pro Glu Pro Ala Phe Gln Arg Ser Ala Ser Thr			
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gct ggg gac atc gcc tgc gcc ttc cgg cct gtc aag tct gtc aag			3159
Ala Gly Asp Ile Ala Cys Ala Phe Arg Pro Val Lys Ser Val Lys			
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atg gct gcc ccg gtc aaa cca cca gcc aca cgg ccc aag ccc act			3204
Met Ala Ala Pro Val Lys Pro Pro Ala Thr Arg Pro Lys Pro Thr			
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Val Phe Pro Lys Thr Asn Ala Thr Ser Pro Gly Val Asn Ser Ser			
	1070	1075	1080
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Thr Ser Pro Gln Ser Thr Asp Lys Ser Cys Thr Val			
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Glu Phe Gly Arg Lys Lys Glu Asn Met Thr Ser Pro Ala Lys Phe Lys
          20           25           30

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Lys Asp Lys Glu Ile Ile Ala Glu Tyr Asp Thr Gln Val Lys Glu Ile
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Arg Ala Gln Leu Thr Glu Gln Met Lys Cys Leu Asp Gln Gln Cys Glu
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72/90

Leu Arg Val Gln Leu Leu Gln Asp Leu Gln Asp Phe Phe Arg Lys Lys
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Ala Glu Ile Glu Met Asp Tyr Ser Arg Asn Leu Glu Lys Leu Ala Glu
 85 90 95

Arg Phe Leu Ala Lys Thr Arg Ser Thr Lys Asp Gln Gln Phe Lys Lys
 100 105 110

Asp Gln Asn Val Leu Ser Pro Val Asn Cys Trp Asn Leu Leu Leu Asn
 115 120 125

Gln Val Lys Arg Glu Ser Arg Asp His Thr Thr Leu Ser Asp Ile Tyr
 130 135 140

Leu Asn Asn Ile Ile Pro Arg Phe Val Gln Val Ser Glu Asp Ser Gly
 145 150 155 160

Arg Leu Phe Lys Lys Ser Lys Glu Val Gly Gln Gln Leu Gln Asp Asp
 165 170 175

Leu Met Lys Val Leu Asn Glu Leu Tyr Ser Val Met Lys Thr Tyr His
 180 185 190

Met Tyr Asn Ala Asp Ser Ile Ser Ala Gln Ser Lys Leu Lys Glu Ala
 195 200 205

Glu Lys Gln Glu Glu Lys Gln Ile Gly Lys Ser Val Lys Gln Glu Asp
 210 215 220

Arg Gln Thr Pro Arg Ser Pro Asp Ser Thr Ala Asn Val Arg Ile Glu
 225 230 235 240

Glu Lys His Val Arg Arg Ser Ser Val Lys Lys Ile Glu Lys Met Lys
 245 250 255

Glu Lys Arg Gln Ala Lys Tyr Thr Glu Asn Lys Leu Lys Ala Ile Lys
 260 265 270

Ala Arg Asn Glu Tyr Leu Leu Ala Leu Glu Ala Thr Asn Ala Ser Val
 275 280 285

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73/90

Phe Lys Tyr Tyr Ile His Asp Leu Ser Asp Leu Ile Asp Gln Cys Cys
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Asp Leu Gly Tyr His Ala Ser Leu Asn Arg Ala Leu Arg Thr Phe Leu
 305 310 315 320

Ser Ala Glu Leu Asn Leu Glu Gln Ser Lys His Glu Gly Leu Asp Ala
 325 330 335

Ile Glu Asn Ala Val Glu Asn Leu Asp Ala Thr Ser Asp Lys Gln Arg
 340 345 350

Leu Met Glu Met Tyr Asn Asn Val Phe Cys Pro Pro Met Lys Phe Glu
 355 360 365

Phe Gln Pro His Met Gly Asp Met Ala Ser Gln Leu Cys Ala Gln Gln
 370 375 380

Pro Val Gln Ser Glu Leu Val Gln Arg Cys Gln Gln Leu Gln Ser Arg
 385 390 395 400

Leu Ser Thr Leu Lys Ile Glu Asn Glu Glu Val Lys Lys Thr Met Glu
 405 410 415

Ala Thr Leu Gln Thr Ile Gln Asp Ile Val Thr Val Glu Asp Phe Asp
 420 425 430

Val Ser Asp Cys Phe Gln Tyr Ser Asn Ser Met Glu Ser Val Lys Ser
 435 440 445

Thr Val Ser Glu Thr Phe Met Ser Lys Pro Ser Ile Ala Lys Arg Arg
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Ala Asn Gln Gln Glu Thr Glu Gln Phe Tyr Phe Thr Lys Met Lys Glu
 465 470 475 480

Tyr Leu Glu Gly Arg Asn Leu Ile Thr Lys Leu Gln Ala Lys His Asp
 485 490 495

Leu Leu Gln Lys Thr Leu Gly Glu Ser Gln Arg Thr Asp Cys Ser Leu
 500 505 510

Ala Arg Arg Ser Ser Thr Val Arg Lys Gln Asp Ser Ser Gln Ala Ile

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74/90

515	520	525
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Gln His Glu Gly Ile Phe Arg Val Ser Gly Ser Gln Val Glu Val Asn 545 550 555 560		
Asp Ile Lys Asn Ala Phe Glu Arg Gly Glu Asp Pro Leu Ala Gly Asp 565 570 575		
Gln Asn Asp His Asp Met Asp Ser Ile Ala Gly Val Leu Lys Leu Tyr 580 585 590		
Phe Arg Gly Leu Glu His Pro Leu Phe Pro Lys Asp Ile Phe His Asp 595 600 605		
Leu Met Ala Cys Val Thr Met Asp Asn Leu Gln Glu Arg Ala Leu His 610 615 620		
Ile Arg Lys Val Leu Leu Val Leu Pro Lys Thr Thr Leu Ile Ile Met 625 630 635 640		
Arg Tyr Leu Phe Ala Phe Leu Asn His Leu Ser Gln Phe Ser Glu Glu 645 650 655		
Asn Met Met Asp Pro Tyr Asn Leu Ala Ile Cys Phe Gly Pro Ser Leu 660 665 670		
Met Ser Val Pro Glu Gly His Asp Gln Val Ser Cys Gln Ala His Val 675 680 685		
Asn Glu Leu Ile Lys Thr Ile Ile Ile Gln His Glu Asn Ile Phe Pro 690 695 700		
Ser Pro Arg Glu Leu Glu Gly Pro Val Tyr Ser Arg Gly Gly Ser Met 705 710 715 720		
Glu Asp Tyr Cys Asp Ser Pro His Gly Glu Thr Thr Pro Val Glu Asp 725 730 735		
Ser Thr Gln Asp Val Thr Ala Glu His His Thr Ser Asp Asp Glu Cys 740 745 750		

Glu Pro Ile Glu Ala Ile Ala Lys Phe Asp Tyr Val Gly Arg Thr Ala
 755 760 765

Arg Glu Leu Ser Phe Lys Lys Gly Ala Ser Leu Leu Leu Tyr Gln Arg
 770 775 780

Ala Ser Asp Asp Trp Trp Glu Gly Arg His Asn Gly Ile Asp Gly Leu
 785 790 795 800

Ile Pro His Gln Tyr Ile Val Val Gln Asp Thr Glu Asp Gly Val Val
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Glu Arg Ser Ser Pro Lys Ser Glu Ile Glu Val Ile Ser Glu Pro Pro
 820 825 830

Glu Glu Lys Val Thr Ala Arg Ala Gly Ala Ser Cys Pro Ser Gly Gly
 835 840 845

His Val Ala Asp Ile Tyr Leu Ala Asn Ile Asn Lys Gln Arg Lys Arg
 850 855 860

Pro Glu Ser Gly Ser Ile Arg Lys Thr Phe Arg Ser Asp Ser His Gly
 865 870 875 880

Leu Ser Ser Ser Leu Thr Asp Ser Ser Ser Pro Gly Val Gly Ala Ser
 885 890 895

Cys Arg Pro Ser Ser Gln Pro Ile Met Ser Gln Ser Leu Pro Lys Glu
 900 905 910

Gly Pro Asp Lys Cys Ser Ile Ser Gly His Gly Ser Leu Asn Ser Ile
 915 920 925

Ser Arg His Ser Ser Leu Lys Asn Arg Leu Asp Ser Pro Gln Ile Arg
 930 935 940

Lys Thr Ala Thr Ala Gly Arg Ser Lys Ser Phe Asn Asn His Arg Pro
 945 950 955 960

Met Asp Pro Glu Val Ile Ala Gln Asp Ile Glu Ala Thr Met Asn Ser
 965 970 975

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76/90

Ala Leu Asn Glu Leu Arg Glu Leu Glu Arg Gln Ser Ser Val Lys His
 980 985 990

Thr Pro Asp Val Val Leu Asp Thr Leu Glu Pro Leu Lys Thr Ser Pro
 995 1000 1005

Val Val Ala Pro Thr Ser Glu Pro Ser Ser Pro Leu His Thr Gln
 1010 1015 1020

Leu Leu Lys Asp Pro Glu Pro Ala Phe Gln Arg Ser Ala Ser Thr
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Ala Gly Asp Ile Ala Cys Ala Phe Arg Pro Val Lys Ser Val Lys
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Met Ala Ala Pro Val Lys Pro Pro Ala Thr Arg Pro Lys Pro Thr
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 ctc cag gac ttc ttc cga aag aag gca gag att gag atg gac tac tcc 96
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 20 25 30

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77/90

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Thr	Lys	Asp	Gln	Gln	Phe	Lys	Lys	Asp	Gln	Asn	Val	Leu	Ser	Pro	Val				
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aac	tgc	tgg	aat	ctc	ctc	tta	aac	cag	gtg	aag	tgg	gaa	agc	agg	gac	240			
Asn	Cys	Trp	Asn	Leu	Leu	Leu	Asn	Gln	Val	Lys	Trp	Glu	Ser	Arg	Asp				
65				70						75					80				
cat	acc	acc	ctg	agt	gac	atc	tac	ctg	aat	aat	atc	att	cct	cga	ttt	288			
His	Thr	Thr	Leu	Ser	Asp	Ile	Tyr	Leu	Asn	Asn	Ile	Ile	Pro	Arg	Phe				
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Ser	Thr	Ala	Asn	Val	Arg	Ile	Glu	Glu	Lys	His	Val	Arg	Arg	Ser	Ser				
			180					185					190						
gtg	aag	aag	att	gag	aag	atg	aag	gag	aag	cac	caa	gcc	aag	tac	acg	624			
Val	Lys	Lys	Ile	Glu	Lys	Met	Lys	Glu	Lys	His	Gln	Ala	Lys	Tyr	Thr				
		195					200					205							
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Glu	Asn	Lys	Leu	Lys	Ala	Ile	Lys	Ala	Gln	Asn	Glu	Tyr	Leu	Leu	Ala				
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ttg	gag	gca	acc	aat	gca	tct	gtc	ttc	aag	tac	tac	atc	cat	gac	cta	720			
Leu	Glu	Ala	Thr	Asn	Ala	Ser	Val	Phe	Lys	Tyr	Tyr	Ile	His	Asp	Leu				
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tct	gac	ctt	att	gat	cag	tgt	tgt	gac	tta	ggc	tac	cat	gca	agt	ctg	768			
Ser	Asp	Leu	Ile	Asp	Gln	Cys	Cys	Asp	Leu	Gly	Tyr	His	Ala	Ser	Leu				
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			260					265					270						

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<210> 167

<211> 333

<212> PRT

<213> Artificial

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PCT/US02/15198

81/90

<220>

<223> Contig

<400> 167

Glu	Cys	Leu	Asp	Gln	Gln	Cys	Glu	Leu	Arg	Val	Gln	Leu	Leu	Gln	Asp
1				5					10					15	

Leu	Gln	Asp	Phe	Phe	Arg	Lys	Lys	Ala	Glu	Ile	Glu	Met	Asp	Tyr	Ser
			20					25					30		

Arg	Asn	Leu	Glu	Lys	Leu	Ala	Glu	His	Phe	Leu	Ala	Lys	Thr	Arg	Ser
		35					40					45			

Thr	Lys	Asp	Gln	Gln	Phe	Lys	Lys	Asp	Gln	Asn	Val	Leu	Ser	Pro	Val
	50					55					60				

Asn	Cys	Trp	Asn	Leu	Leu	Leu	Asn	Gln	Val	Lys	Trp	Glu	Ser	Arg	Asp
65					70					75					80

His	Thr	Thr	Leu	Ser	Asp	Ile	Tyr	Leu	Asn	Asn	Ile	Ile	Pro	Arg	Phe
				85					90					95	

Val	Gln	Val	Ser	Glu	Asp	Ser	Gly	Arg	Leu	Phe	Lys	Lys	Ser	Lys	Glu
			100					105					110		

Val	Gly	Gln	Gln	Leu	Gln	Asp	Asp	Leu	Met	Lys	Val	Leu	Asn	Glu	Leu
		115					120					125			

Tyr	Ser	Val	Met	Lys	Thr	Tyr	His	Met	Tyr	Asn	Ala	Asp	Ser	Ile	Ser
	130					135					140				

Ala	Gln	Ser	Lys	Leu	Lys	Glu	Ala	Glu	Lys	Gln	Glu	Glu	Lys	Gln	Ile
145					150					155					160

Gly	Lys	Ser	Val	Lys	Gln	Glu	Asp	Arg	Gln	Thr	Pro	Arg	Ser	Pro	Asp
				165					170					175	

Ser	Thr	Ala	Asn	Val	Arg	Ile	Glu	Glu	Lys	His	Val	Arg	Arg	Ser	Ser
			180					185					190		

Val	Lys	Lys	Ile	Glu	Lys	Met	Lys	Glu	Lys	His	Gln	Ala	Lys	Tyr	Thr
			195				200					205			

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82/90

Glu Asn Lys Leu Lys Ala Ile Lys Ala Gln Asn Glu Tyr Leu Leu Ala
 210 215 220

Leu Glu Ala Thr Asn Ala Ser Val Phe Lys Tyr Tyr Ile His Asp Leu
 225 230 235 240

Ser Asp Leu Ile Asp Gln Cys Cys Asp Leu Gly Tyr His Ala Ser Leu
 245 250 255

Asn Arg Ala Leu Arg Thr Phe Leu Ser Ala Glu Leu Asn Leu Glu Gln
 260 265 270

Ser Lys His Glu Gly Leu Asp Ala Ile Glu Asn Ala Val Glu Asn Leu
 275 280 285

Asp Ala Thr Ser Asp Lys Gln Arg Leu Met Glu Met Tyr Asn Asn Val
 290 295 300

Phe Cys Pro Pro Met Lys Phe Glu Val Phe Ser Pro Thr Leu Gly Asp
 305 310 315 320

Met Ala Phe Pro Ala Leu Cys Pro Ala Ala Cys Pro Glu
 325 330

<210> 168
 <211> 494
 <212> DNA
 <213> Artificial

<220>
 <223> Probe

<400> 168
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 gctgacagta taagataaag agggaaatga tgggggatgg gtcattgtaaa gggagaactt 420
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494

<210> 169

<211> 616

<212> PRT

<213> Homo sapiens

<400> 169

Met	Leu	His	Asn	Leu	Asn	Gln	Gln	Arg	Lys	Asn	Gly	Gly	Arg	Phe	Cys
1				5					10					15	

Asp	Val	Leu	Leu	Arg	Val	Gly	Asp	Glu	Ser	Phe	Pro	Ala	His	Arg	Ala
			20					25					30		

Val	Leu	Ala	Ala	Cys	Ser	Glu	Tyr	Phe	Glu	Ser	Val	Phe	Ser	Ala	Gln
		35					40					45			

Leu	Gly	Asp	Gly	Gly	Ala	Ala	Asp	Gly	Gly	Pro	Ala	Asp	Val	Gly	Gly
	50					55					60				

Ala	Thr	Ala	Ala	Pro	Gly	Gly	Gly	Ala	Gly	Gly	Ser	Arg	Glu	Leu	Glu
65					70					75					80

Met	His	Thr	Ile	Ser	Ser	Lys	Val	Phe	Gly	Asp	Ile	Leu	Asp	Phe	Ala
				85					90					95	

Tyr	Thr	Ser	Arg	Ile	Val	Val	Arg	Leu	Glu	Ser	Phe	Pro	Glu	Leu	Met
			100					105					110		

Thr	Ala	Ala	Lys	Phe	Leu	Leu	Met	Arg	Ser	Val	Ile	Glu	Ile	Cys	Gln
		115					120					125			

Glu	Val	Ile	Lys	Gln	Ser	Asn	Val	Gln	Ile	Leu	Val	Pro	Pro	Ala	Arg
	130					135					140				

Ala	Asp	Ile	Met	Leu	Phe	Arg	Pro	Pro	Gly	Thr	Ser	Asp	Leu	Gly	Phe
145					150					155					160

Pro	Leu	Asp	Met	Thr	Asn	Gly	Ala	Ala	Leu	Ala	Ala	Asn	Ser	Asn	Gly
				165					170					175	

Ile	Ala	Gly	Ser	Met	Gln	Pro	Glu	Glu	Glu	Ala	Ala	Arg	Ala	Ala	Gly
			180					185					190		

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84/90

Ala Ala Ile Ala Gly Gln Ala Ser Leu Pro Val Leu Pro Gly Val Asp
 195 200 205

Arg Leu Pro Met Val Ala Gly Pro Leu Ser Pro Gln Leu Leu Thr Ser
 210 215 220

Pro Phe Pro Ser Val Ala Ser Ser Ala Pro Pro Leu Thr Gly Lys Arg
 225 230 235 240

Gly Arg Gly Arg Pro Arg Lys Ala Asn Leu Leu Asp Ser Met Phe Gly
 245 250 255

Ser Pro Gly Gly Leu Arg Glu Ala Gly Ile Leu Pro Cys Gly Leu Cys
 260 265 270

Gly Lys Val Phe Thr Asp Ala Asn Arg Leu Arg Gln His Glu Ala Gln
 275 280 285

His Gly Val Thr Ser Leu Gln Leu Gly Tyr Ile Asp Leu Pro Pro Pro
 290 295 300

Arg Leu Gly Glu Asn Gly Leu Pro Ile Ser Glu Asp Pro Asp Gly Pro
 305 310 315 320

Arg Lys Arg Ser Arg Thr Arg Lys Gln Val Ala Cys Glu Ile Cys Gly
 325 330 335

Lys Ile Phe Arg Asp Val Tyr His Leu Asn Arg His Lys Leu Ser His
 340 345 350

Ser Gly Glu Lys Pro Tyr Ser Cys Pro Val Cys Gly Leu Arg Phe Lys
 355 360 365

Arg Lys Asp Arg Met Ser Tyr His Val Arg Ser His Asp Gly Ser Val
 370 375 380

Gly Lys Pro Tyr Ile Cys Gln Ser Cys Gly Lys Gly Phe Ser Arg Pro
 385 390 395 400

Asp His Leu Asn Gly His Ile Lys Gln Val His Thr Ser Glu Arg Pro
 405 410 415

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85/90

His Lys Cys Gln Thr Cys Asn Ala Ser Phe Ala Thr Arg Asp Arg Leu
 420 425 430

Arg Ser His Leu Ala Cys His Glu Asp Lys Val Pro Cys Gln Val Cys
 435 440 445

Gly Lys Tyr Leu Arg Ala Ala Tyr Met Ala Asp His Leu Lys Lys His
 450 455 460

Ser Glu Gly Pro Ser Asn Phe Cys Ser Ile Cys Asn Arg Glu Gly Gln
 465 470 475 480

Lys Cys Ser His Gln Asp Pro Ile Glu Ser Ser Asp Ser Tyr Gly Asp
 485 490 495

Leu Ser Asp Ala Ser Asp Leu Lys Thr Pro Glu Lys Gln Ser Ala Asn
 500 505 510

Gly Ser Phe Ser Cys Asp Met Ala Val Pro Lys Asn Lys Met Glu Ser
 515 520 525

Asp Gly Glu Lys Lys Tyr Pro Cys Pro Glu Cys Gly Ser Phe Phe Arg
 530 535 540

Ser Lys Ser Tyr Leu Asn Lys His Ile Gln Lys Val His Val Arg Ala
 545 550 555 560

Leu Gly Gly Pro Leu Gly Asp Leu Gly Pro Ala Leu Gly Ser Pro Phe
 565 570 575

Ser Pro Gln Gln Asn Met Ser Leu Leu Glu Ser Phe Gly Phe Gln Ile
 580 585 590

Val Gln Ser Ala Phe Ala Ser Ser Leu Val Asp Pro Glu Val Asp Gln
 595 600 605

Gln Pro Met Gly Pro Glu Gly Lys
 610 615

<210> 170

<211> 440

<212> PRT

<213> Homo sapiens

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PCT/US02/15198

86/90

<400> 170

Met	Glu	Gly	Val	Leu	Tyr	Lys	Trp	Thr	Asn	Tyr	Leu	Ser	Gly	Trp	Gln
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Pro	Arg	Trp	Phe	Leu	Leu	Cys	Gly	Gly	Ile	Leu	Ser	Tyr	Tyr	Asp	Ser
			20					25					30		

Pro	Glu	Asp	Ala	Trp	Lys	Gly	Cys	Lys	Gly	Ser	Ile	Gln	Met	Ala	Val
		35					40					45			

Cys	Glu	Ile	Gln	Val	His	Ser	Val	Asp	Asn	Thr	Arg	Met	Asp	Leu	Ile
50						55					60				

Ile	Pro	Gly	Glu	Gln	Tyr	Phe	Tyr	Leu	Lys	Ala	Arg	Ser	Val	Ala	Glu
65					70					75					80

Arg	Gln	Arg	Trp	Leu	Val	Ala	Leu	Gly	Ser	Ala	Lys	Ala	Cys	Leu	Thr
				85					90					95	

Asp	Ser	Arg	Thr	Gln	Lys	Glu	Lys	Glu	Phe	Ala	Glu	Asn	Thr	Glu	Asn
			100					105					110		

Leu	Lys	Thr	Lys	Met	Ser	Glu	Leu	Arg	Leu	Tyr	Cys	Asp	Leu	Leu	Val
		115					120					125			

Gln	Gln	Val	Asp	Lys	Thr	Lys	Glu	Val	Thr	Thr	Thr	Gly	Val	Ser	Asn
		130				135					140				

Ser	Glu	Glu	Gly	Ile	Asp	Val	Gly	Thr	Leu	Leu	Lys	Ser	Thr	Cys	Asn
145					150					155					160

Thr	Phe	Leu	Lys	Thr	Leu	Glu	Glu	Cys	Met	Gln	Ile	Ala	Asn	Ala	Ala
				165					170					175	

Phe	Thr	Ser	Glu	Leu	Leu	Tyr	Arg	Thr	Pro	Pro	Gly	Ser	Pro	Gln	Leu
			180					185					190		

Ala	Met	Leu	Lys	Ser	Ser	Lys	Met	Lys	His	Pro	Ile	Ile	Pro	Ile	His
		195					200					205			

Asn	Ser	Leu	Glu	Arg	Gln	Met	Glu	Leu	Ser	Thr	Cys	Glu	Asn	Gly	Ser
	210					215					220				

Leu Asn Met Glu Ile Asn Gly Glu Glu Glu Ile Leu Met Lys Asn Lys
 225 230 235 240

Asn Ser Leu Tyr Leu Lys Ser Ala Glu Ile Asp Cys Ser Ile Ser Ser
 245 250 255

Glu Glu Asn Thr Asp Asp Asn Ile Thr Val Gln Gly Glu Ile Arg Lys
 260 265 270

Glu Asp Gly Met Glu Asn Leu Lys Asn His Asp Asn Asn Leu Thr Gln
 275 280 285

Ser Gly Ser Asp Ser Ser Cys Ser Pro Glu Cys Leu Trp Glu Glu Gly
 290 295 300

Lys Glu Val Ile Pro Thr Phe Phe Ser Thr Met Asn Thr Ser Phe Ser
 305 310 315 320

Asp Ile Glu Leu Leu Glu Asp Ser Gly Ile Pro Thr Glu Ala Phe Leu
 325 330 335

Ala Ser Cys Tyr Ala Val Val Pro Val Leu Asp Lys Leu Gly Pro Thr
 340 345 350

Val Phe Ala Pro Val Lys Met Asp Leu Val Gly Asn Ile Lys Lys Val
 355 360 365

Asn Gln Lys Tyr Ile Thr Asn Lys Glu Glu Phe Thr Thr Leu Gln Lys
 370 375 380

Ile Val Leu His Glu Val Glu Ala Asp Val Ala Gln Val Arg Asn Ser
 385 390 395 400

Ala Thr Glu Ala Leu Leu Trp Leu Lys Arg Gly Leu Lys Phe Leu Lys
 405 410 415

Gly Phe Leu Thr Glu Val Lys Asn Gly Glu Lys Asp Ile Gln Thr Ala
 420 425 430

Leu Arg Asn Pro Thr Glu Asn Thr
 435 440

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PCT/US02/15198

88/90

<210> 171
 <211> 537
 <212> PRT
 <213> Homo sapiens

<400> 171

Met Glu Arg Val Asn Asp Ala Ser Cys Gly Pro Ser Gly Cys Tyr Thr
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Tyr Gln Val Ser Arg His Ser Thr Glu Met Leu His Asn Leu Asn Gln
 20 25 30

Gln Arg Lys Asn Gly Gly Arg Phe Cys Asp Val Leu Leu Arg Val Gly
 35 40 45

Asp Glu Ser Phe Pro Ala His Arg Ala Val Leu Ala Ala Cys Asn Glu
 50 55 60

Tyr Phe Glu Ser Val Phe Ser Ala Gln Leu Gly Asp Gly Gly Ala Ala
 65 70 75 80

Asp Gly Gly Pro Ala Asp Val Gly Gly Ala Thr Ala Ala Pro Gly Gly
 85 90 95

Gly Ala Gly Gly Ser Arg Glu Leu Glu Met His Thr Ile Ser Ser Lys
 100 105 110

Val Phe Gly Asp Ile Leu Asp Phe Ala Tyr Thr Ser Arg Ile Val Val
 115 120 125

Arg Leu Glu Ser Phe Pro Glu Leu Met Thr Ala Ala Lys Phe Leu Leu
 130 135 140

Met Arg Ser Val Ile Glu Ile Cys Gln Glu Val Ile Lys Gln Ser Asn
 145 150 155 160

Val Gln Ile Leu Val Pro Pro Ala Arg Ala Asp Ile Met Leu Phe Arg
 165 170 175

Pro Pro Gly Thr Ser Asp Leu Gly Phe Pro Leu Asp Met Thr Asn Gly
 180 185 190

Ala Ala Leu Ala Ala Asn Ser Asn Gly Ile Ala Gly Ser Met Gln Pro
 195 200 205

Glu Glu Glu Ala Ala Arg Ala Ala Gly Ala Ala Ile Ala Gly Gln Ala
 210 215 220

Ser Leu Pro Val Leu Pro Gly Val Asp Arg Leu Pro Met Val Ala Gly
 225 230 235 240

Pro Leu Ser Pro Gln Leu Leu Thr Ser Pro Phe Pro Ser Val Ala Ser
 245 250 255

Ser Ala Leu Pro Leu Thr Gly Lys Arg Gly Arg Gly Arg Pro Arg Lys
 260 265 270

Ala Asn Leu Leu Asp Ser Met Phe Gly Ser Pro Gly Gly Leu Arg Glu
 275 280 285

Ala Gly Ile Leu Pro Cys Gly Leu Cys Gly Lys Val Phe Thr Asp Ala
 290 295 300

Asn Arg Leu Arg Gln His Glu Ala Gln His Gly Val Thr Ser Leu Gln
 305 310 315 320

Leu Gly Tyr Ile Asp Leu Pro Pro Pro Arg Leu Gly Glu Asn Gly Leu
 325 330 335

Pro Ile Ser Glu Asp Pro Asp Gly Pro Arg Lys Arg Ser Arg Thr Arg
 340 345 350

Lys Gln Val Ala Cys Glu Ile Cys Gly Lys Ile Phe Arg Asp Val Tyr
 355 360 365

His Leu Asn Arg His Lys Leu Ser His Ser Gly Glu Lys Pro Tyr Ser
 370 375 380

Cys Pro Val Cys Gly Leu Arg Phe Lys Lys Lys Asp Arg Met Ser Tyr
 385 390 395 400

His Val Arg Ser His Asp Gly Ser Val Gly Lys Pro Tyr Ile Cys Gln
 405 410 415

Ser Cys Gly Lys Gly Phe Ser Arg Pro Asp His Leu Asn Gly His Ile
 420 425 430

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Lys Gln Val His Thr Ser Glu Arg Pro His Lys Cys Gln Val Trp Val
435 440 445

Gly Ser Ser Ser Gly Leu Pro Pro Leu Glu Pro Leu Pro Ser Asp Leu
450 455 460

Pro Ser Trp Asp Phe Ala Gln Pro Ala Leu Trp Arg Ser Ser His Ser
465 470 475 480

Val Pro Asp Thr Ala Phe Ser Leu Ser Leu Lys Lys Ser Phe Pro Ala
485 490 495

Leu Glu Asn Leu Gly Pro Ala His Ser Ser Asn Thr Leu Phe Cys Pro
500 505 510

Ala Pro Pro Gly Tyr Leu Arg Gln Gly Trp Thr Thr Pro Glu Gly Ser
515 520 525

Arg Ala Phe Thr Gln Trp Pro Val Gly
530 535

CLAIMS

We claim:

- 5 1. An isolated molecule comprising bases 2 to 8 of SEQ ID NO: 19 and also comprising bases 13 to 16 of SEQ ID NO: 19, wherein one or more of said bases, which are each at the 1-position of a sugar moiety, independently and optionally have –OH, –OC₁₋₆Alkyl, halo, amino, azido, nitro or phenyl at the 2-position of said sugar moiety, and wherein one or more of said bases are optionally further modified to result in a modified base.
- 10 2. An isolated molecule comprising bases 2 to 8 of SEQ ID NO: 97 and also comprising bases 13 to 16 of SEQ ID NO: 97, wherein one or more of said bases, which are each at the 1-position of a sugar moiety, independently and optionally have –OH, –OC₁₋₆Alkyl, halo, amino, azido, nitro or phenyl at the 2-position of said sugar moiety, and wherein
- 15 one or more of said bases are optionally further modified to result in a modified base.
3. The molecule of claims 1 or 2, wherein said bases are not further modified.
4. The molecule of claim 3, wherein bases 2, 4 and 5 of SEQ ID NO: 19 are each
- 20 thymine, and base 16 of SEQ ID NO: 97 is uracil.
5. The molecule of claims 1 or 2, further comprising bases 8 to 11 of SEQ ID NO: 5.
6. The molecule of claim 4, further comprising bases 8 to 15 of SEQ ID NO: 5.
- 25 7. The molecule of claims 1 or 2, wherein at least one but not all of the 2-positions of said sugar moieties have –OH, –OC₁₋₆Alkyl, halo, amino, azido, nitro or phenyl.

8. A composition comprising the molecule of claim 1 and the molecule of claim 2, wherein said bases are not optionally further modified.
9. The molecule of claim 4, wherein the 2-position of the sugar moiety of each of bases 6
5 and 7 is $-\text{OCH}_3$.
10. The molecule of claim 4, comprising SEQ ID NO: 5.
11. The molecule of claim 4, comprising SEQ ID NO: 6.
10
12. The molecule of claim 4, consisting of SEQ ID NO: 5.
13. The molecule of claim 4, consisting of SEQ ID NO: 6.
- 15 14. A hammerhead ribozyme, comprising the molecule of claims 5 or 7.
15. A method of facilitating the induction of apoptosis in a cell, comprising introducing in said cell the molecule of claim 1.
- 20 16. The method of claim 15, wherein said cell is resistant to apoptosis.
17. The method of claim 16, wherein said cell is a cancer cell.
18. The method of claim 17, further comprising contacting said cell with an apoptosis
25 inducing agent.
19. The method of claim 18, wherein said agent is Fas.

20. A method of facilitating the induction of apoptosis in a cell, comprising introducing in said cell the molecule of claim 2.
21. The method of claim 20, wherein said cell is resistant to apoptosis.
- 5 22. The method of claim 21, wherein said cell is a cancer cell.
23. The method of claim 22, further comprising contacting said cell with an apoptosis inducing agent.
- 10 24. The method of claim 23, wherein said agent is Fas.
25. A method of facilitating the induction of apoptosis in a cell, comprising introducing in said cell the molecules of claims 1 and 2.
- 15 26. The method of claim 25, wherein said cell is resistant to apoptosis.
27. The method of claim 26, wherein said cell is a cancer cell.
- 20 28. The method of claim 27, further comprising contacting said cell with an apoptosis inducing agent.
29. The method of claim 28, wherein said agent is Fas.
- 25 30. An isolated compound comprising SEQ ID NO: 158 or an amino acid sequence with 98% or more identity with SEQ ID NO: 158 .

31. An isolated compound comprising amino acids 1 to 247 of SEQ ID NO: 167 or an amino acid sequence with 98% or more identity with amino acids 1 to 247 of SEQ ID NO: 167 .

- 5 32. The isolated compound of claim 31, comprising SEQ ID NO: 167 or an amino acid sequence with 98% or more identity with SEQ ID NO: 167.

33. A method of identifying a molecule that promotes induction of apoptosis in a cell, comprising:

10

a. contacting said molecule with the a compound comprising 10 or more contiguous amino acids of SEQ ID NO: 158 or 10 or more contiguous amino acids of amino acids 1 to 247 of SEQ ID NO: 167, wherein said molecule binds said compound;

- 15 b. introducing said molecule into a cell; and

c. measuring the level of apoptosis in said cell, where an increase in the level of apoptosis in said cell indicates that said molecule promotes induction of apoptosis.

- 20 34. An isolated molecule comprising SEQ ID NO: 146 or a molecule with 95% or more identity with SEQ ID NO: 146.

35. The isolated molecule of claim 34, comprising SEQ ID NO: 148 or a molecule with 95% or more identity with SEQ ID NO: 148.

25

36. The isolated molecule of claim 34, comprising SEQ ID NO: 150 or a molecule with 95% or more identity with SEQ ID NO: 150.

37. The isolated molecule of claim 34, comprising SEQ ID NO: 152 or a molecule with 95% or more identity with SEQ ID NO: 152.

38. The isolated molecule of claim 34, comprising SEQ ID NO: 155 or a molecule with 95% or more identity with SEQ ID NO: 155.

39. The isolated molecule of claim 34, comprising SEQ ID NO: 157 or a molecule with 95% or more identity with SEQ ID NO: 157 .

40. The isolated molecule of claim 34, comprising SEQ ID NO: 166 or a molecule with 95% or more identity with SEQ ID NO: 166.

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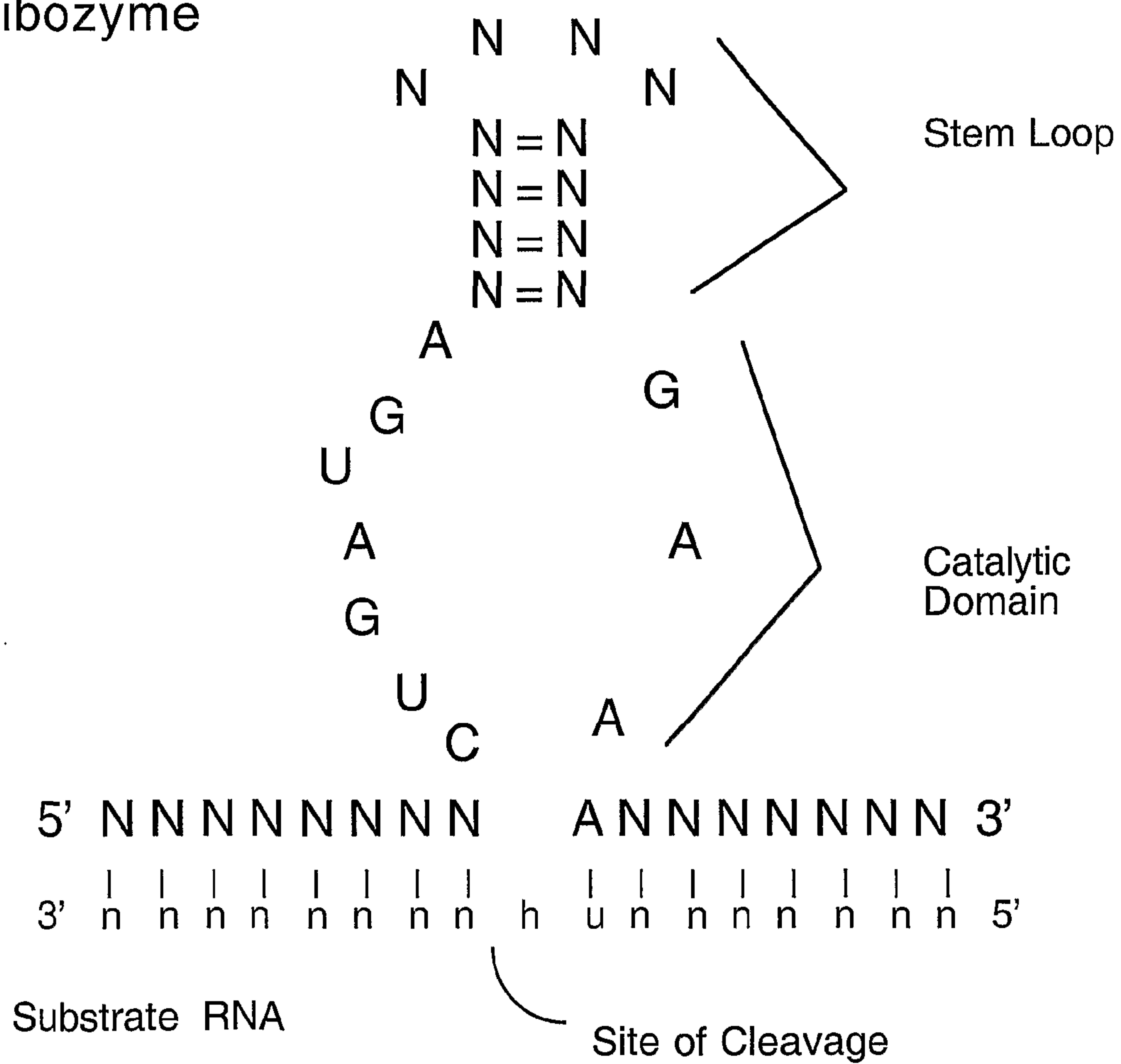
Hammerhead
Ribozyme

Figure 2

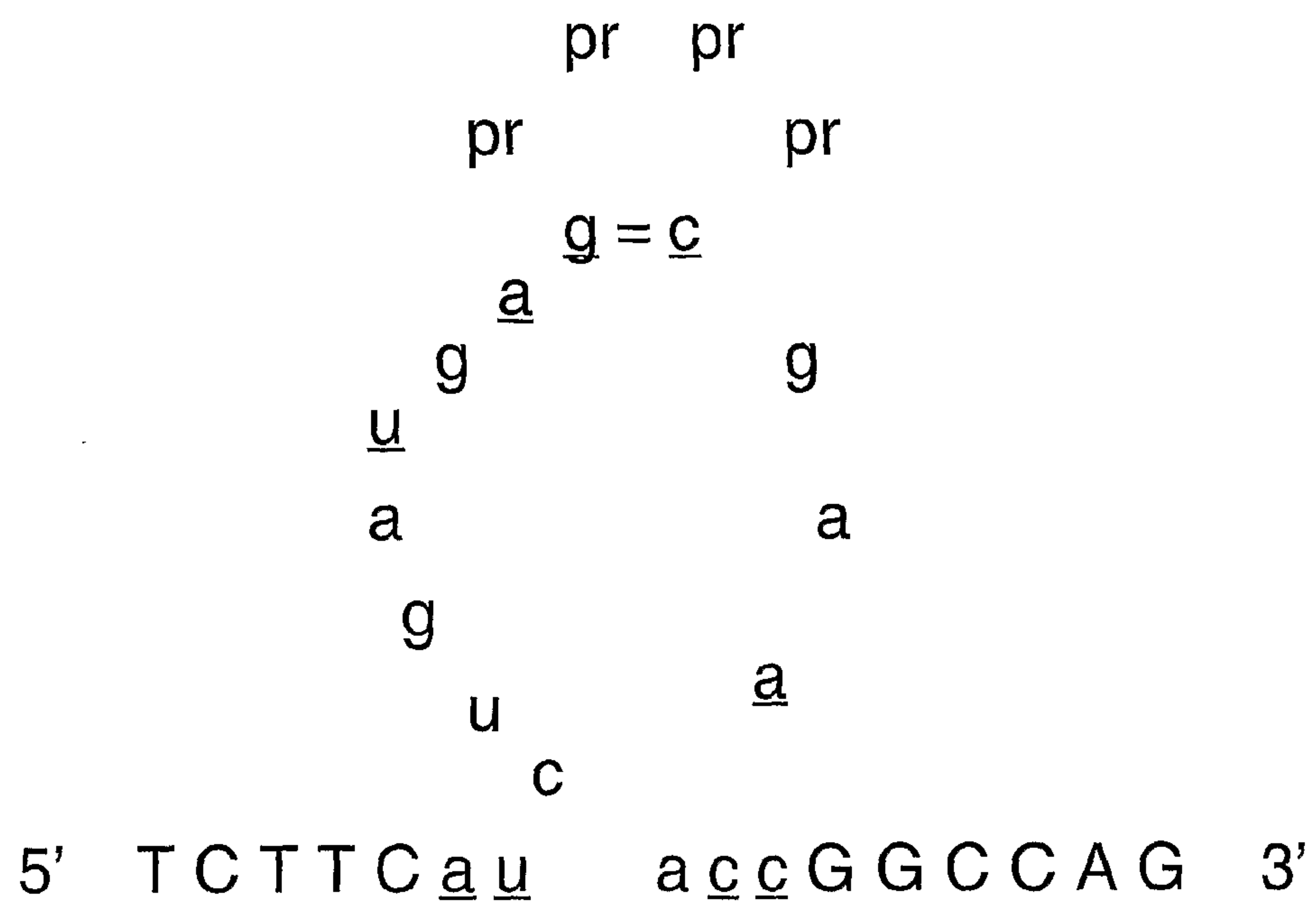


Figure 3

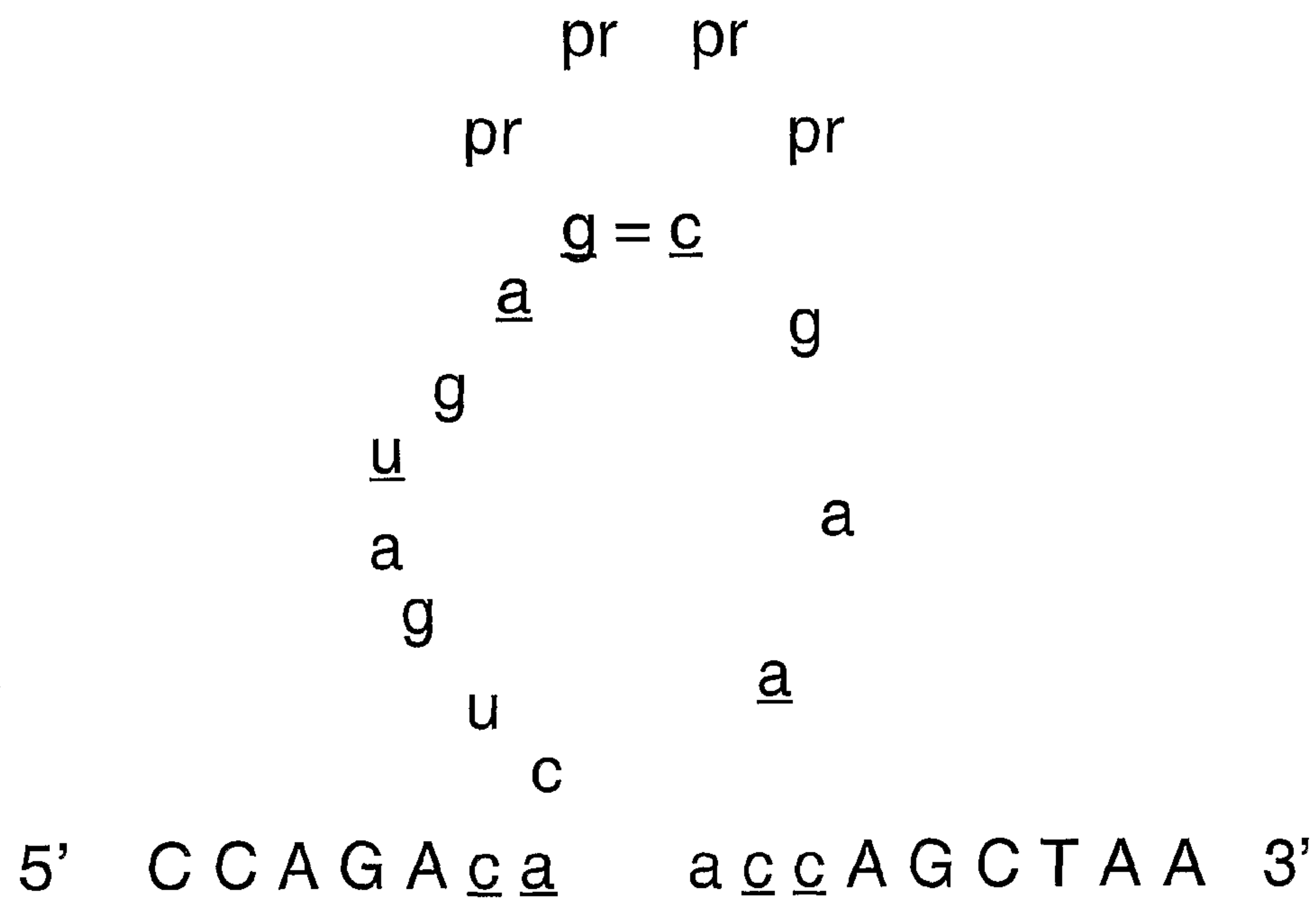


Figure 4

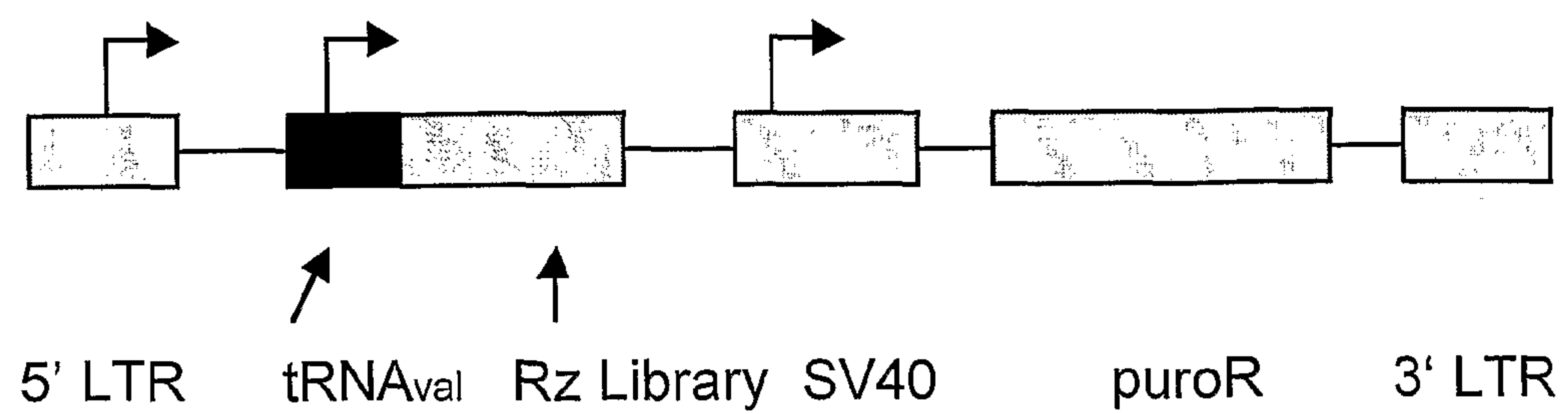


Figure 5

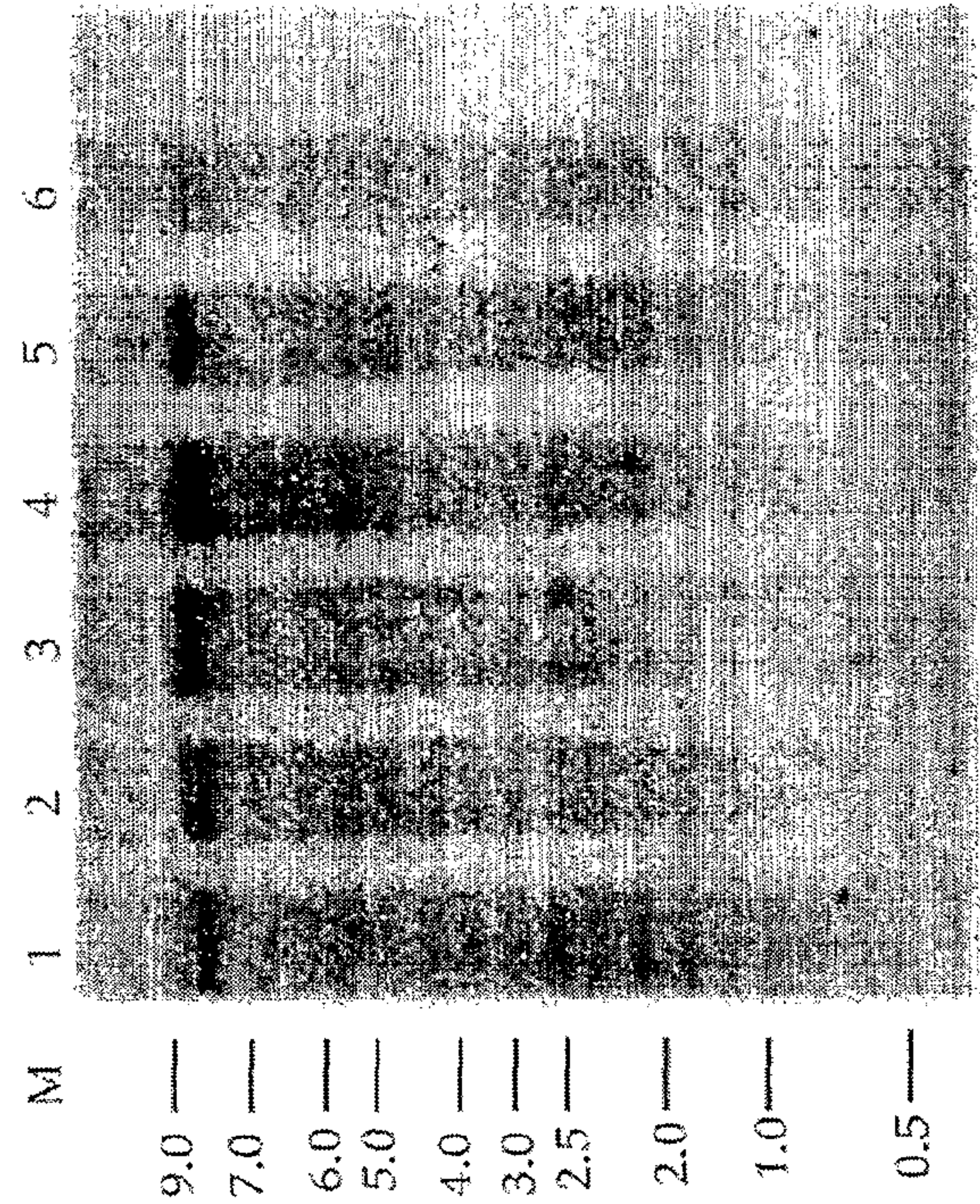


Figure 7

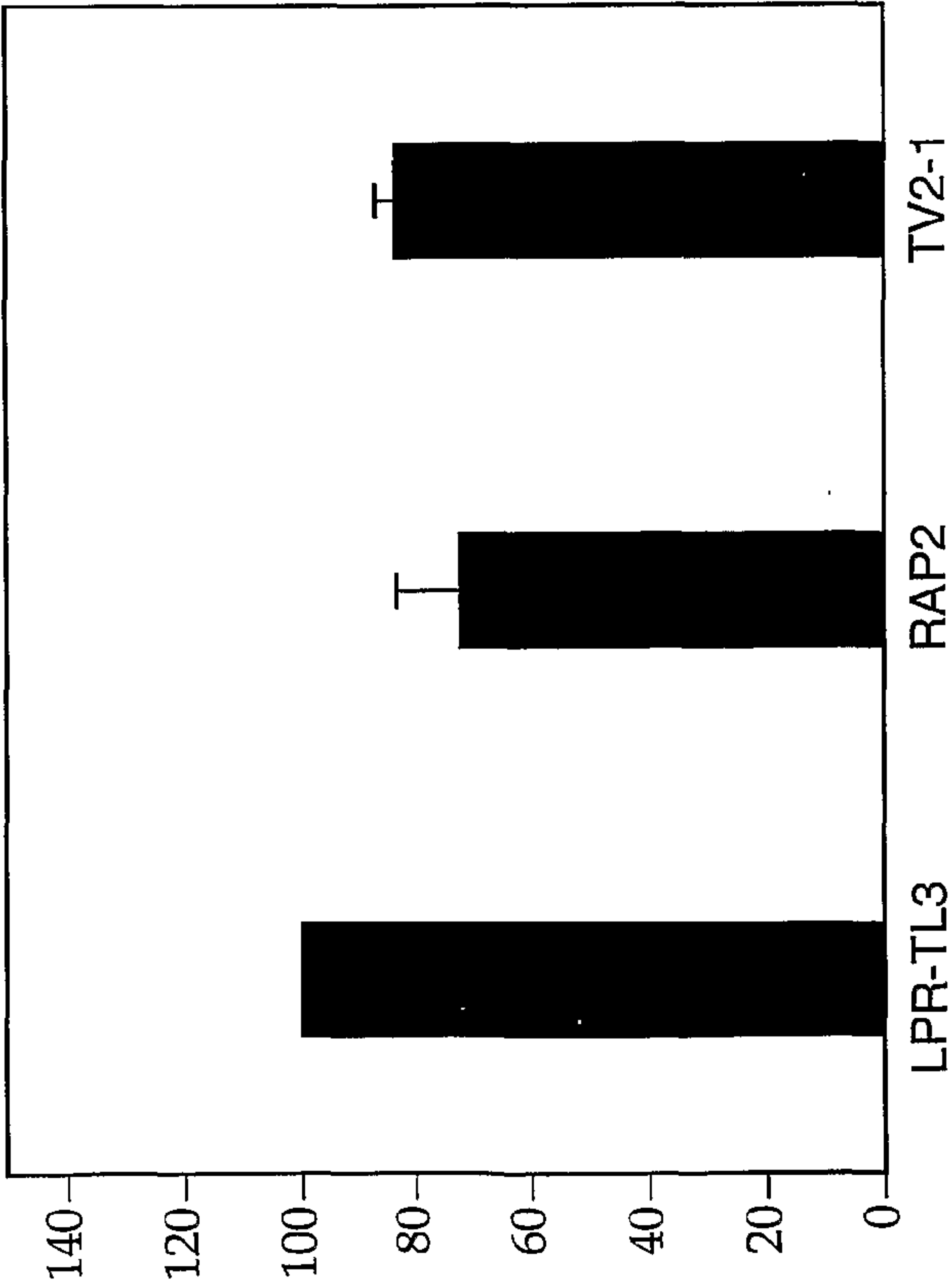


Figure 6

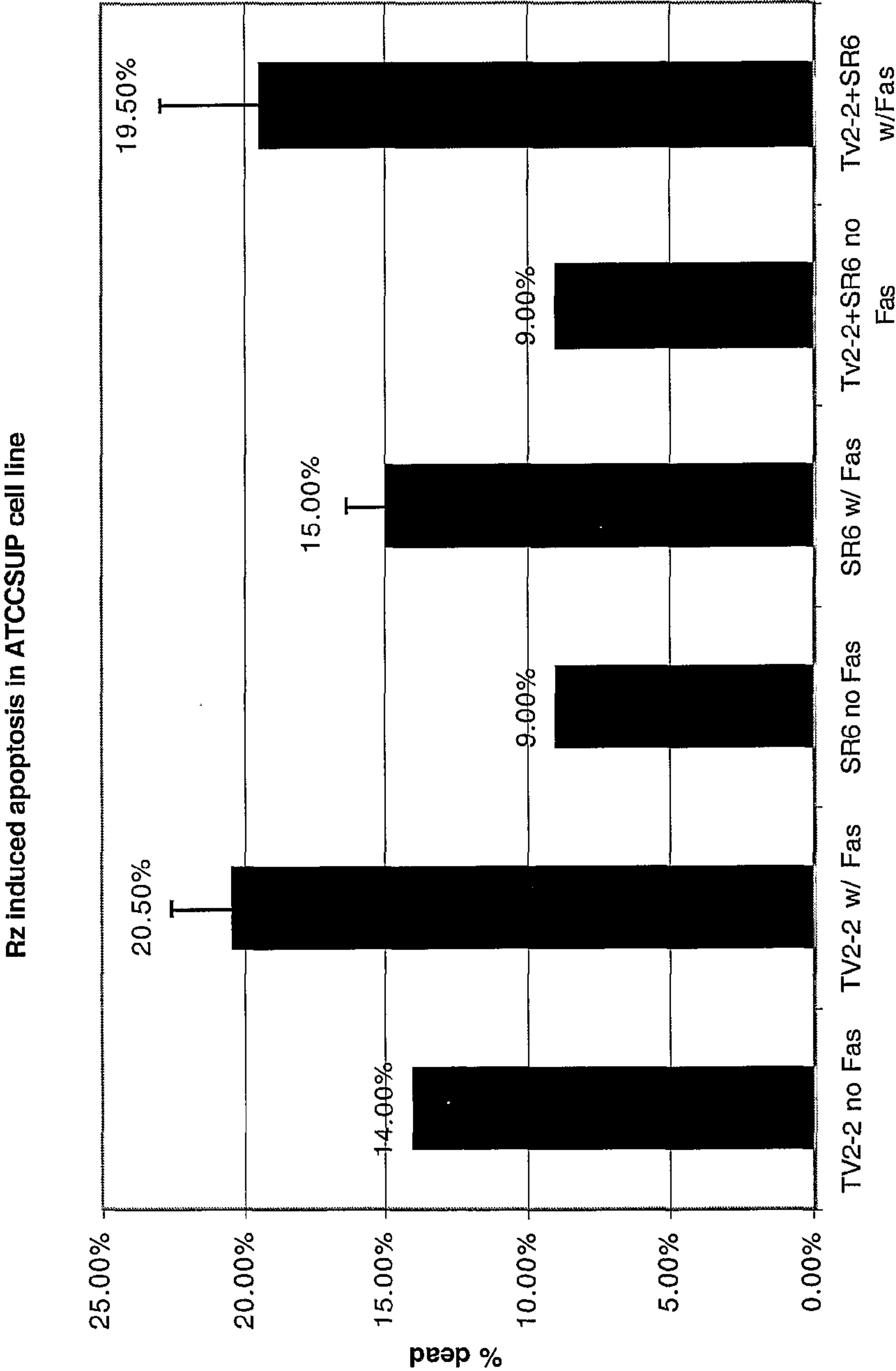


Figure 8

