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(54) Title: THE USE OF EUKARYOTIC GENES AFFECTING SPINDLE FORMATION OR MICROTUBULE FUNCTION DURING CELL DIVISION FOR DIAGNOSIS AND TREATMENT OF PROLIFERATIVE DISEASES

(57) Abstract: The present invention relates to the significant functional role of several C. elegans genes and of their corresponding gene products in spindle formation or microtubule function during cell division that could be identified by means of RNA-mediated interference (RNAi) and to the identification and isolation of functional orthologs of said genes including all biologically functional derivatives thereof The invention further relates to the use of said genes and gene products (including said orthologs) in the development or isolation of anti-proliferative agents, particularly their use in appropriate screening assays, and their use for diagnosis and treatment of proliferative and other diseases. In particular, the invention relates to the use of small interfering RNAs derived from said genes for the treatment of proliferative diseases.

The use of eukaryotic genes affecting spindle formation or microtubule function during cell division for diagnosis and treatment of proliferative diseases

The present invention relates to the use of agents interfering with mitotic spindle ("spindle") formation or microtubule function during cell division for the treatment of diseases, especially proliferative diseases.

Metazoan cell division (mitosis) consists of an extremely complex, highly regulated set of cellular processes which must be tightly co-ordinated, perfectly timed, and closely monitored in order to ensure the correct delivery of cellular materials to daughter cells. Defects in these processes are known to cause a wide range of so-called proliferative diseases, including all forms of cancer. Since cell division represents one of the few, if not the only cellular process that is common to the aetiology of all forms of cancer, its specific inhibition has long been recognised as a preferred site of therapeutic intervention.

Although mitotic inhibitor drugs are recognised as one of the most promising classes of chemotherapeutic agents, screening attempts to find new drug candidates in this class have been undermined by the strong inherent tendency of such screens to identify agents that target a single protein, tubulin. Tubulin polymerises to form microtubules, the primary cytoskeletal elements needed for mitotic spindle function and chromosome segregation. Microtubules as such, however, are ubiquitously needed in almost all cell types, whether dividing or not, a fact which therefore explains many of the unwanted side effects caused by anti-tubulin drugs.

Perhaps the best known example of a highly successful anti-neoplastic drug that targets tubulin is paclitaxel, and its marketed derivative, Taxol. Its applicability has indeed been seriously limited by difficulties in determining an adequate dosing regimen due to a range of problematic side effects. Taxol treatment has resulted in anaphylaxis and severe

hypersensitivity reactions characterised by dyspnea and hypotension requiring treatment, angioedema, and generalised urticaria in 2-4% of patients in clinical trials. Although Taxol is administered after pretreatment with corticosteroids, fatal reactions have occurred. Severe conductance abnormalities resulting in life-threatening cardiac arrhythmia occur in less than 1 percent of patients and must be treated by insertion of a pacemaker. Taxol can cause fetal harm or fetal death in pregnant women. Furthermore, administration is commonly accompanied by tachycardia, hypotension, flushing, skin reactions and shortness-of-breath (mild dyspnea). Reasons for these strong side-effects may be that since tubulin does not only play an essential role in spindle formation, but also plays significant roles in other cellular processes like for instance cytoskeleton generation and intracellular protein transport.

Consequently, although Taxol has been hailed by many as the most successful new anti-cancer therapeutic of the last three decades, there is still a need for anti-cancer drugs that do not show the disadvantages of Taxol.

Therefore, the problem underlying the present invention resides in providing improved potent anti-cancer drugs, particularly with less severe side effects.

The problem is solved by the use of an isolated nucleic acid molecule comprising a sequence selected from the group of sequences consisting of:

a) the nucleic acid sequences presented in SEQ ID NO. 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59;

b) nucleic acid sequences encoding polypeptides that exhibit a sequence identity with the protein encoded by a nucleic acid according to a) of at least 25 % over 100 residues and/or which are detectable in a computer aided search using the BLAST sequence analysis programs with an e-value of at most 10^{-5},

c) sequences of nucleic acid molecules which are capable of hybridizing with the nucleic acid molecules with sequences corresponding to (a) or (b) under conditions of medium or high stringency,

d) the antisense-sequence of any of the sequences as defined in (a), (b) or (c),

e) fragments of (a), (b), (c) or (d),

f) double-stranded RNA or single-stranded RNA in the antisense or sense direction corresponding to any of the sequences as defined in (a), (b), (c), (d), or (e)

for the manufacture of a medicament for the inhibition of spindle formation or microtubule function during cell division.

The present invention is based on the concept to provide agents interfering with spindle formation or microtubule function during cell division. Spindle formation or microtubule function during cell division are essential parts of cell division.

As a consequence of the present invention, target genes important for spindle formation or microtubule function during cell division were identified, leaving the general cellular appearance and therefore general cellular microtubule functions intact.

Thus, as the target proteins are involved in a cell division-specific process, the inhibition of these target proteins results in an efficient impairment of mitosis as well as in a reduced number of side effects caused by the inhibition of other significant cellular processes.

The present invention discloses for the first time for a variety of proteins and genes that they are involved in spindle formation or microtubule function during cell division. Although cell division and microtubules have already been thoroughly studied, the present invention provides several classes of target genes, corresponding gene products and other agents that had previously not been implicated in cell division, particularly not in spindle formation or microtubule function during cell division.

The newly identified function of these target genes and their corresponding gene products, any homologs, orthologs and derivatives thereof enables their use in the development of a wide range of medicaments against proliferative diseases including cancer. These medicaments could be used in treatment of proliferative diseases, particularly in those cases where the disorder relates to cell division, regulation of cell division, or is dependent on spindle formation or microtubule function during cell division. Furthermore, the newly identified function enables the use in diagnosis and the development of diagnostic agents.

For the identification of target genes being involved in spindle formation or microtubule function during cell division, a large-scale RNAi technique-based screen was performed for 19514 (that means 99.7%) of the predicted open reading frames in the C. elegans genome. For the performance of this large-scale screen double-stranded RNA corresponding to the individual open reading frames was produced and micro-injected into adult C. elegans hermaphrodites, and the resulting embryos were analysed 24 hours later using time-lapse DIC microscopy.

The nematode C. elegans exhibits an almost entirely translucent body throughout its development, thereby offering unparalleled microscopic access for exquisitely detailed cytological documentation, even for the earliest steps of embryogenesis. This important feature, along with its short life cycle (3-5 days), its ease of cultivation, and its low maintenance costs, has helped make C. elegans arguably the best studied of all metazoans. Also, sequence data are now available for over 97% of the C. elegans genome (C. elegans Sequencing Consortium. Genome sequence of the nematode C. elegans: a platform for investigating biology. Science 282, 2012-2018 (1998)). Thus, C. elegans is an ideal organism for applying the new technique of RNA-mediated interference (RNAi). This technique consists in the targeted, sequence-specific inhibition of gene expression, as mediated by the introduction into an adult worm of double-stranded RNA (dsRNA) molecules corresponding to portions of the coding sequences of interest (Fire et al., Potent and specific genetic interference by double-stranded RNA in Caenorhabditis elegans. Nature 391, 806-811 (1998)). For the vast majority of C. elegans genes tested to date, this has been shown to yield a sequence-specific inhibition of the targeted gene's expression, accompanied by clearly detectable loss of function phenotypes in the treated worm's F1 progeny (and even in some cases, in the treated worm itself).

In the context of the present invention, a screening assay in C. elegans based on 'genomic RNA mediated interference (RNAi)' combined with a highly probative microscopic assay for documenting the first rounds of embryonic cell division was used (Sulston et al., The embryonic cell lineage of the nematode Caenorhabditis elegans. Dev. Biol. 100, 64-119 (1983); Gönczy et al., Dissection of cell division processes in the one cell stage Caenorhabditis elegans embryo by mutational analysis. J Cell Biol 144, 927-946 (1999)).

With this combination of techniques a selected gene and also a variety of selected genes can be functionally characterized with unprecedented speed and efficiency.

The DIC microscopy generated movies were analyzed to identify those samples whereby cell division was altered or disrupted. In order to perform the analysis in a robust, consistent and reproducible fashion, each movie was analyzed with regard to 47 different parameters. In other words, 47 features of normal cell division (i.e. cell division in wild type worms) were scored for every RNAi phenotype generated by the genome-wide application of RNAi across the entire C. elegans genome.

A powerful confirmation and validation of the DIC assay, and the depth of information that the assays yield, was that equivalent phenotypes were found to represent closely related proteins, proteins within the same family or functionally equivalent proteins. In other words, if the RNAi-induced phenotypes of two separately analyzed genes are the same, it is very likely that the two proteins are either within the same protein class or share a similar function or at the very least, are both involved in the same biological mechanism or process. Therefore, the screen can be used to class or group proteins according to their function. Consequently, any genes that give rise to similar RNAi phenotypes are related and are justified to be considered within single functional classes.

"Nucleic acids" according to the present invention comprises all known nucleic acids such as DNA, RNA, peptide nucleic acids, morpholinos, and nucleic acids with backbone structures other than phosphodiesters, such as phosphothiates or phosphoramidates.

"Microtubule function during cell division" according to the present invention relates to any function of microtubules during cell division, including microtubular structure, disassembly and reassembly, and motor-based defects. Motor-based defects according to the present invention comprise any defects of transport along microtubules related to defects of microtubule-associated transport molecules. Preferably, "microtubule function during cell division" relates to microtubule function specific for cell division, i.e. not to microtubule functions essential for non-dividing cells.

"Inhibition of spindle formation or microtubule function during cell division" according to the present invention includes halting or arresting as well as retarding or slowing down of spindle formation or microtubule function during cell division.

In a preferred embodiment of the invention, the nucleic acid molecule comprises a nucleic acid molecule with a sequence selected from the group of sequences as presented in SEQ ID NO. 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59. Preferably, the nucleic acid molecule consists of a nucleic acid molecule with a sequence selected from said group of sequences.

The term "comprise" preferably refers to nucleic acids in which the nucleic acids with the described sequences are functionally relevant, e.g. for diagnostic use or therapeutic use, such as vectors for therapeutical use or expression of corresponding RNAs or proteins. Preferably, any additional nucleic acids upstream or downstream of the sequence are not longer than 20 kb. More preferred, the term "comprise" does not relate to large constructs accidentally including the sequence, such as genomic BAC or YAC clones.

In detail, the individual SEQ ID No. denotes the following sequences:

SEQ ID NO. 1	the nucleotide sequence of the C. elegans gene C13F10.2 (Wormbase accession No. CE08144)
SEQ ID NO. 2	the deduced amino acid sequence of the C. elegans gene C13F10.2 (Wormbase accession No. CE08144)
SEQ ID NO. 3	the nucleotide sequence of the human ortholog of C13F10.2 (GenBank accession No. NM_024069)
SEQ ID NO. 4	the deduced amino acid sequence of the human ortholog of C13F10.2 (GenBank accession No. NP_076974)
SEQ ID NO. 5	the nucleotide sequence of the Drosophila homolog of C13F10.2 (GenBank accession No. AE003541)
SEQ ID NO. 6	the deduced amino acid sequence of the Drosophila homolog of C13F10.2 (GenBank accession No. AAF49911)

SEQ ID NO. 7 the nucleotide sequence of the C. elegans gene C25A1.9 (Wormbase accession No. CE18532)

SEQ ID NO. 8 the deduced amino acid sequence of the C. elegans gene C25A1.9 (Wormbase accession No. CE18532)

SEQ ID NO. 9 the nucleotide sequence of the human ortholog of C25A1.9 (GenBank accession No. NM_017917)

SEQ ID NO. 10 the deduced amino acid sequence of the human ortholog of C25A1.9 (GenBank accession No. NP_060387)

SEQ ID NO. 11 the nucleotide sequence of the C. elegans gene F54B3.3 (Wormbase accession No. CE03405)

SEQ ID NO. 12 the deduced amino acid sequence of the C. elegans gene F54B3.3 (Wormbase accession No. CE03405)

SEQ ID NO. 13 the nucleotide sequence of the human ortholog of F54B3.3 (GenBank accession No. NM_018188)

SEQ ID NO. 14 the deduced amino acid sequence of the human ortholog of F54B3.3 (GenBank accession No. NP_060658)

SEQ ID NO. 15 the nucleotide sequence of the mouse homolog of F54B3.3 (GenBank accession No. XM_109399)

SEQ ID NO. 16 the deduced amino acid sequence of the mouse homolog of F54B3.3 (GenBank accession No. XP_109399)

SEQ ID NO. 17 the nucleotide sequence (corresponding to the mRNA) of the rat homolog of F54B3.3 (GenBank accession No. NM_053864)

SEQ ID NO. 18 the deduced amino acid sequence of the rat homolog of F54B3.3 (GenBank accession No. NP_446316 or P46462)

SEQ ID NO. 19 the nucleotide sequence of the Drosophila ortholog of F54B3.3 (GenBank accession No. AE003712)

SEQ ID NO. 20 the deduced amino acid sequence of the Drosophila ortholog of F54B3.3 (GenBank accession No. AAF55289)

SEQ ID NO. 21 the nucleotide sequence of the yeast homolog of F54B3.3 (GenBank accession No. NC_001148.1, base pairs 610476 to 612719)

SEQ ID NO. 22 the deduced amino acid sequence of the yeast homolog of F54B3.3 (GenBank accession No. NP_015349)

SEQ ID NO. 23 the nucleotide sequence of the C. elegans gene F08B6.2 (Wormbase accession No. CE20656)

SEQ ID NO. 24 the deduced amino acid sequence of the C. elegans gene F08B6.2 (Wormbase accession No. CE20656)

SEQ ID NO. 25 the nucleotide sequence of the human ortholog of F08B6.2 (GenBank accession No. NM_016541)

SEQ ID NO. 26 the deduced amino acid sequence of the human ortholog of F08B6.2 (GenBank accession No. NP_057625)

SEQ ID NO. 27 the nucleotide sequence (corresponding to the mRNA) of the rat homolog of F08B6.2 (GenBank accession No. NM_139185)

SEQ ID NO. 28 the deduced amino acid sequence of the rat homolog of F08B6.2 (GenBank accession No. NP_631924 or AAA73553)

SEQ ID NO. 29 the nucleotide sequence of the Drosophila homolog of F08B6.2 (GenBank accession No. AE003624)

SEQ ID NO. 30 the deduced amino acid sequence of the Drosophila homolog of F08B6.2 (GenBank accession No. AAF52761)

SEQ ID NO. 31 the nucleotide sequence of the C. elegans gene CD4.4 (Wormbase accession No. CE16952)

SEQ ID NO. 32 the deduced amino acid sequence of the C. elegans gene CD4.4 (Wormbase accession No. CE16952)

SEQ ID NO. 33 the nucleotide sequence of a human ortholog of CD4.4 (GenBank accession No. NM_024667)

SEQ ID NO. 34 the deduced amino acid sequence of a human ortholog of CD4.4 (GenBank accession No. NP_078943)

SEQ ID NO. 35 the nucleotide sequence (corresponding to the mRNA) of a human ortholog of CD4.4 (GenBank accession No. AL834261)

SEQ ID NO. 36 the deduced amino acid sequence of a human ortholog of CD4.4 (GenBank accession No. CAD38936)

SEQ ID NO. 37 the nucleotide sequence of the Drosophila homolog of CD4.4 (GenBank accession No. AE003603)

SEQ ID NO. 38 the deduced amino acid sequence of the Drosophila homolog of CD4.4 (GenBank accession No. AF52060)

SEQ ID NO. 39 the nucleotide sequence of the C. elegans gene ZK546.1 (Wormbase accession No. CE28524)

SEQ ID NO. 40 the deduced amino acid sequence of the C. elegans gene ZK546.1 (Wormbase accession No. CE28524)

SEQ ID NO. 41 the nucleotide sequence of the human ortholog of ZK546.1 (GenBank accession No. NM_015888)

SEQ ID NO. 42 the deduced amino acid sequence of the human ortholog of ZK546.1 (GenBank accession No. NP_056972)

SEQ ID NO. 43 the nucleotide sequence of the rat homolog of ZK546.1 (GenBank accession No. NM_031745)

SEQ ID NO. 44 the deduced amino acid sequence of the rat homolog of ZK546.1 (GenBank accession No. XP_113933)

SEQ ID NO. 45 the nucleotide sequence of the mouse homolog of ZK546.1 (GenBank accession No. XM_109474)

SEQ ID NO. 46 the deduced amino acid sequence of the mouse homolog of ZK546.1 (GenBank accession No. XP_109474)

SEQ ID NO. 47 the nucleotide sequence of the Drosophila homolog of ZK546.1 (GenBank accession No. AE003655)

SEQ ID NO. 48 the deduced amino acid sequence of the Drosophila homolog of ZK546.1 (GenBank accession No. AAF53605)

SEQ ID NO. 49 the nucleotide sequence of the yeast homolog of ZK546.1 (GenBank accession No. NC_001136, base pairs 345664 to 351036)

SEQ ID NO. 50 the deduced amino acid sequence of the yeast homolog of ZK546.1 (GenBank accession No. NP_010225)

SEQ ID NO. 51 the nucleotide sequence of the C. elegans gene C56C10.3 (Wormbase accession No. CE0256)

SEQ ID NO. 52 the deduced amino acid sequence of the C. elegans gene C56C10.3 (Wormbase accession No. CE0256)

SEQ ID NO. 53 the nucleotide sequence of the human ortholog of C56C10.3 (GenBank accession No. XM_059282)

SEQ ID NO. 54 the deduced amino acid sequence of the human ortholog of C56C10.3 (GenBank accession No. XP_059282)

SEQ ID NO. 55 the nucleotide sequence of the mouse ortholog of C56C10.3 (GenBank accession No. NM_029362)

SEQ ID NO. 56 the deduced amino acid sequence of the mouse ortholog of C56C10.3 (GenBank accession No. NP_083638)

SEQ ID NO. 57 the nucleotide sequence of the Drosophila ortholog of C56C10.3 (GenBank accession No. AE003834)

SEQ ID NO. 58 the deduced amino acid sequence of the Drosophila ortholog of C56C10.3 (GenBank accession No. AAF58977)

SEQ ID NO. 59 the nucleotide sequence of a yeast homolog of C56C10.3 (GenBank accession No. NC_001144, base pairs 194453 to 195175)

SEQ ID NO. 60 the deduced amino acid sequence of a yeast homolog of C56C10.3 (GenBank accession No. NP_013125)

Unless otherwise specified, the manipulations of nucleic acids and polypeptides/-proteins can be performed using standard methods of molecular biology and immunology (see, e.g. Maniatis et al. (1989), Molecular cloning: A laboratory manual, Cold Spring Harbor Lab., Cold Spring Harbor, NY; Ausubel, F.M. et al. (eds.) "Current protocols in Molecular Biology". John Wiley and Sons, 1995; Tijssen, P., Practice and Theory of Enzyme Immunoassays, Elsevier Press, Amsterdam, Oxford, New York, 1985).

The present invention describes genes identified as having essential functions in cell division in the model organism C. elegans. The basis for performing research in model organisms is that the newly discovered functions for the genes in C. elegans will be conserved in other species including humans. Cell division as well as spindle formation or microtubule function during cell division are highly conserved during evolution and therefore the approach of discovering a gene function in C. elegans and using the

information to characterise or assign functions for human homologs or orthologs is well justified.

One theme of conservation is that the gene function can be conserved with substantial divergence of sequence. In the present invention this theme of conservation is not defined. However, if other genes are discovered to have functions that result in the gene product being identified as the same gene product as those claimed in the present invention then the present claims also apply to such genes.

However, the most frequent theme of conservation of genes during evolution is that the gene sequence is conserved. This theme of conservation is particularly frequent for genes involved in highly conserved processes such as cell division. This means that the DNA nucleotide sequence or the protein coding sequence of the gene are very similar in different species, which in turn suggests that the function of the gene is the same in the different species.

Therefore, in a further preferred embodiment, the nucleic acid molecule has a sequence that encodes a polypeptide exhibiting a sequence identity with a protein encoded by SEQ ID NO. 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59 of at least 25 % over 100 residues, preferably of at least 30 % over 100 residues, more preferably of at least 50 % over 100 residues, particularly of at least 70 % over 100 residues on amino acid level.

These very high sequence similarities are usually shown by polypeptides which are orthologs or homologs of the above sequences. A homolog is a protein with similar sequence from the same or another species (an homolog's sequence similarity originates from a speciation event or from a gene duplication, i.e. a homolog is a related protein in any species or the same protein in another species). A subgroup of homologs are defined as orthologs. An ortholog is essentially the same protein as the one it is compared to, but it is derived from another species (an ortholog's sequence similarity originates from a speciation event rather than a gene duplication). It is known to a person skilled in the art, that in a conserved process such as cell division, homologous and orthologous proteins, particularly orthologous proteins, are very likely to serve the same biological function. In

the present case, the most relevant biological function is the involvement in, particularly the requirement for, spindle formation or microtubule function during cell division.

Advantageously, it could be shown that human orthologs of the C.elegans genes identified in the context of this invention are required for proliferation, cell survival and mitosis (see Example 11). This finding indicates that the human orthologs are required for spindle formation and microtubule function during cell division and can be used in the context of diagnosis and treatment of proliferative diseases.

The person skilled in the art is familiar with different methods and criteria to identify homologs and orthologs. In the context of the present invention, homologs and orthologs were identified based on sequence similarity according to the procedure described in Example 1.

The nucleic acid molecule may also comprise a sequence that is detectable in a computer aided database search/alignment with an e-value of at most 10^{-5}, preferably with an e-value of at most 10^{-12}, particularly with an e-value of at most 10^{-20} or fragments thereof, whereby the database sequences are compared to the sequences as defined under a). The nucleic acid molecule may also comprise a sequence that is considered an ortholog according to the criteria of the present invention (see Example 1). Generally, the grade of sequence identity can be calculated by any software program that is capable to perform protein sequence alignments known in the art. Hereby it is also included that identical amino acid regions are interrupted by gaps that can be variable in their length.

For this kind of analysis or alignments the "BLAST sequence analysis programs" are particularly preferred. The "BLAST sequence analysis programs" which may be used for sequence analysis are publically available and known to anyone skilled in the art. Known analysis programs for sequence alignments, particularly the "BLAST sequence analysis programs", calculate so called "e-values" to characterize the grade of homology between the compared sequences. Generally, a small e-value characterizes a high sequence similarity, whereas larger e-values characterize lower sequence similarity.

The degree of similarity required for the sequence variant will depend upon the intended use of the sequence. It is well within the capability of a person skilled in the art to effect mutational, insertional and deletional mutations which are designed to improve the function of the sequence or otherwise provide a methodological advantage.

The aforementioned grades of sequence identities with proteins encoded by the above SEQ IDs are characteristic for such polypeptides that are strongly homologous to the above sequences, in particular for polypeptides that are "orthologous" or "homologous" to the polypeptides of a).

Table 1 shows the e-values that have been calculated for the alignments on amino acid level with homologs and orthologs of the corresponding C. elegans gene. Hereby, e-values lower than 10^{-5} on amino acid level characterize homologs of the corresponding C. elegans genes. If the C. elegans gene is itself a reciprocal hit of the identified homolog with an e-value of less than 10^{-5}, then the homolog is identified as an ortholog (see also Example 1).

C. elegans gene	e-value for the alignment with the C. elegans gene on amino acid level
C13F10.2	Human orthol. $6*10^{-13}$ Drosoph. orthol. $1*10^{-19}$
C25A1.9	Human orthol. $8*10^{-6}$
F54B3.3	Human orthol. $1*10^{-170}$ Mouse homol. $3*10^{-15}$ Rat homol. $8*10^{-15}$ Drosoph. orthol. $1*10^{-163}$ Yeast homol. $8*10^{-15}$
F08B6.2	Human orthol. $4*10^{-6}$ Rat homol. $2*10^{-6}$ Drosoph. orthol. $2*10^{-11}$
CD4.4	Human orthol. $1*10^{-9}$ (GenBank Acc.No. NP_078943) Human orthol. $2*10^{-8}$ (GenBank Acc.No.

	CAD38936) Drosoph. orthol. $2*10^{-9}$
ZK546.1	Human orthol. $1*10^{-12}$ Mouse homol. $4*10^{-6}$ Rat homol. $7*10^{-11}$ Drosoph. homol. $2*10^{-9}$ Yeast homol. $3*10^{-14}$
C56C10.3	Human orthol. $2*10^{-60}$ Mouse orthol. $3*10^{-60}$ Drosoph. orthol. $4*10^{-51}$ Yeast homol. $3*10^{-28}$

Table 1: Sequence similarities between the C. elegans genes C13F10.2, C25A1.9, F54B3.3, F08B6.2, CD4.4, ZK546.1, C56C10.3 and their human, mouse, rat, Drosophila, and yeast homologs and orthologs.

According to a further preferred embodiment, the nucleic acid molecule comprises a nucleotide sequence which is capable of hybridizing with the nucleic acid sequences of (a) or (b) under conditions of medium/high stringency.

In such hybrids, duplex formation and stability depend on substantial complementarity between the two strands of the hybrid and a certain degree of mismatch can be tolerated. Therefore, the nucleic acid molecules and probes of the present invention may include mutations (both single and multiple), deletions, insertions of the above identified sequences, and combinations thereof, as long as said sequence variants still have substantial sequence similarity to the original sequence which permits the formation of stable hybrids with the target nucleotide sequence of interest.

Suitable experimental conditions for determining whether a given DNA or RNA sequence "hybridizes" to a specified polynucleotide or oligonucleotide probe involve presoaking of the filter containing the DNA or RNA to examine for hybridization in 5 x SSC (sodium chloride/sodium citrate) buffer for 10 minutes, and prehybridization of the filter in a

solution of 5 x SSC, 5 x Denhardt's solution, 0,5 % SDS and 100 mg/ml of denaturated sonicated salmon sperm DNA (Maniatis et al.,1989), followed by hybridization in the same solution containing a concentration of 10 ng/ml of a random primed (Feinberg, A.P. and Vogelstein, B. (1983), Anal. Biochem. 132:6-13), ^{32}P-dCTP-labeled (specific activity > 1 x 10^9 cpm/µg) probe for 12 hours at approximately 45°C. The filter is then washed twice for 30 minutes in 2 x SSC, 0,5% SDS at at least 55°C (low stringency), at least 60°C (medium stringency), preferably at least 65°C (medium/high stringency), more preferably at least 70°C (high stringency) or most preferably at least 75°C (very high stringency). Molecules to which the probe hybridizes under the chosen conditions are detected using an x-ray film or a "phosphor imager".

According to a further preferred embodiment, the nucleic acid molecules may also have the antisense-sequence of any of the sequences as defined in (a), (b) or (c).

According to a further preferred embodiment, fragments of the nucleic acid molecules as described above may be used.

The term "fragment" as used according to the present invention can have different meanings depending on the molecule and purpose referred to. A person skilled in the art knows how to choose appropriate fragments for the relevant purpose. Preferably, a fragment should be specific for the sequence it is derived from. The meaning of the term "specific" is known in the art. Preferably, specific in this context means that in a BLAST search performed with the sequence fragment, the original sequence (from which the fragment is derived) would be identified with a lower e-value than all other sequences relevant in the context of the current use (e.g. all other sequences of nucleic acids present in the investigated sample). More preferably, the original sequence should be identified with the lowest e-value compared to all other sequences identified. Alternatively, "specific" means that, under the applied conditions, the fragment binds only to the nucleic acid molecule it is derived from. The criterion of specificity is usually achieved by fragments larger than 15 nucleotides, preferably larger than 19 nucleotides. Preferably, the fragments are chosen from sequence regions of high complexity. Low complexity regions can be identified by database searches or low complexity filters available in standard sequence analysis programs.

"Biologically active" fragments or derivatives can be generated by a person skilled in the art. Hereby, the fragments or derivatives should have a similar "biological function" as the nucleic acid they are derived from. According to the present invention the most relevant biological function is the involvement in, inhibition of, activation of, or requirement for spindle formation or microtubule function during cell division.

The isolated nucleic acid molecules defined as under (a) to (e) may be used for influencing cell division and/or cell proliferation, particularly by inhibiting spindle formation or microtubule function during cell division, either in vitro or in vivo.

Inhibition of spindle formation or microtubule function during cell division using said nucleic acid molecules can be achieved by different ways familiar to the person skilled in the art. For example, the isolated nucleic acid molecules may be inserted downstream of a strong promotor to overexpress the corresponding protein or polypeptide. Overexpression of the protein or polypeptide may lead to suppression of the endogenous protein's biological function. By introducing deletions or other mutations into the nucleic acids, or by using suitable fragments, it is possible to generate sequences encoding dominant-negative peptides or polypeptides. Such dominant-negative peptides or polypeptides can inhibit the function of the corresponding endogenous protein.

Certain nucleic acids can be used to inhibit expression (transcription and/or translation) of the endogenous genes to inhibit spindle formation or microtubule function during cell division. E.g. peptide nucleic acids comprising sequences as identified above can suppress expression of the corresponding endogenous gene by forming DNA triplex structures with the gene. Other nucleic acids, such as antisense morpholino oligonucleotides or ribozymes, can be used to interfere with RNA transcribed from the endogenous gene.

The application of automated gene synthesis provides an opportunity for generating sequence variants of the naturally occurring genes. It will be appreciated that polynucleotides coding for synthetic variants of the corresponding amino acid sequences can be generated which, for example, will result in one or more amino acids substitutions, deletions or additions. Also, nucleic acid molecules comprising one or more synthetic

nucleotide derivatives (including morpholinos) which provide said nucleotide sequence with a desired feature, e.g. a reactive or detectable group, can be prepared. Synthetic derivatives with desirable properties may also be included in the corresponding polypeptides. All such derivatives and fragments of the above identified genes and gene products showing at least part of the biological activity or biological function of the naturally occurring sequences or which are still suitable to be used, for example, as probes for, e.g. identification of homologous genes or gene products, are included within the scope of the present invention. Also included are such derivatives and fragments whose activity or function is counteracting to the biological activity or biological function of the naturally occurring sequences, e.g. derivatives and fragments that encode dominant-negative molecules.

Having herein provided the nucleotide sequences of various genes functionally involved in spindle formation or microtubule function during cell division, it will be appreciated that automated techniques of gene synthesis and/or amplification may be used to isolate said nucleic acid molecules in vitro. Because of the length of some coding sequences, application of automated synthesis may require staged gene construction, in which regions of the gene up to about 300 nucleotides in length are synthesized individually and then ligated in correct succession for final assembly. Individually sythesized gene regions can be amplified prior to assembly, using polymerase chain reaction (PCR) technology. The technique of PCR amplification may also be used to directly generate all or part of the final genes/nucleic acid molecules. In this case, primers are synthesized which will be able to prime the PCR amplification of the final product, either in one piece or in several pieces that may be ligated together. For this purpose, either cDNA or genomic DNA may be used as the template for the PCR amplification. The cDNA template may be derived from commercially available or self-constructed cDNA libraries.

According to a further preferred embodiment, the invention relates to the use of the above identified nucleic acid molecules or fragments thereof in form of RNA, particularly antisense RNA and double-stranded RNA, for the manufacture of a medicament for the inhibition of spindle formation or microtubule function during cell division. Also ribozymes can be generated for the above identified sequences and used to degrade RNA transcribed from the corresponding endogenous genes.

As stated above, double-stranded RNA oligonucleotides effect silencing of the expression of gene(s) which are highly homologous to either of the RNA strands in the duplex. Recent discoveries had revealed that this effect, called RNA interference (RNAi), that had been originally discovered in C. elegans, can also be observed in mammalian, particularly in human cells. Thus, inhibition of a specific gene function by RNA interference can also be performed in mammalian cells, particularly also in human cells

As shown in Fig. 1, the inhibition of a nucleic acid molecule as defined under (a) to (f) by RNAi in C. elegans inhibits cell division by impairing spindle formation or microtubule function during cell division.

Particularly preferred is the use of these RNA molecules in a therapeutical application of the RNAi technique, particularly in humans or in human cells.

An RNAi technique particularly suited for mammalian cells makes use of double-stranded RNA oligonucleotides known as "small interfering RNA" (siRNA).

Therefore, according to a further preferred embodiment, the invention relates to the use of nucleic molecules comprising small interfering RNA with a sequence corresponding to any of the sequences identified above.

These siRNA molecules can be used for the therapeutical silencing of the expression of the genes of the invention comprising nucleic acid sequences as defined under (a) to (f), in mammalian cells, particularly in human cells, particularly for the therapy of a proliferative disease.

The inhibition of a specific target gene in mammals is achieved by the introduction of an siRNA-molecule having a sequence that is specific (see above) for the target gene into the mammalian cell. The siRNAs comprise a first and a second RNA strand, both hybridized to each other, wherein the sequence of the first RNA strand is a fragment of one of the sequences as defined in a) to f) and wherein the sequence of the second RNA strand is the antisense-strand of the first RNA strand. The siRNA-molecules may possess a

characteristic 2- or 3-nucleotide 3'-overhanging sequence. Each strand of the siRNA molecule preferably has a length of 19 to 31 nucleotides.

The siRNAs can be introduced into the mammalian cell by any suitable known method of cell transfection, particularly lipofection, electroporation or microinjection. The RNA oligonucleotides can be generated and hybridized to each other in vitro or in vivo according to any of the known RNA synthesis methods.

The possibility to inhibit gene expression of disease-associated genes also in mammalian cells and in particular in human cells, make siRNAs or vector systems capable of producing siRNAs, having the sequence of those disease-associated genes, an interesting therapeutical agent for pharmaceutical compositions. Particularly siRNAs having sequences as defined in the present invention or that are homologous or orthologous to one of those genes can be used for the manufacture of medicaments for the inhibition of spindle formation or microtubule function during cell division and for the therapy of diseases, particularly proliferative diseases (see below). Similarly, nucleic acid vectors capable of producing those siRNAs can be used for the manufacture of such medicaments.

In another embodiment, the invention relates to the use of a nucleic acid molecule as defined above, wherein the nucleic acid molecule is contained in at least one nucleic acid expression vector which is capable of producing a double-stranded RNA-molecule comprising a sense-RNA-stand and an antisense-RNA-strand under suitable conditions, wherein each RNA-strand, independently from the other, has a length of 19 to 31 nucleotides.

In this alternative method (also described in Tuschl, Nature Biotechnology, Vol. 20, pp. 446-448), vector systems capable of producing siRNAs instead of the siRNAs themselves are introduced into the mammalian cell for downregulating gene expression.

The preferred lengths of the RNA-strands produced by such vectors correspond to those preferred for siRNAs in general (see below).

"Suitable conditions" for the production of the above double-stranded RNA-molecule are all in vivo or in vitro conditions that according to the state of art allow the expression of a first and a second RNA-strand with the above sequences and lengths that – when hybridized - form a double-stranded RNA-molecule. Particularly preferred "suitable conditions" for the production of the above double-stranded RNA-molecule are the "in vivo conditions" in a living human or animal cell or the "in vitro conditions" in cultured human or animal cells.

The "nucleic acid expression vector" may be an extrachromosomal entity, the replication of which is independent of chromosomal replication, e.g. a plasmid. Alternatively, the vector may be one which, when introduced into a host cell, particularly into a mammalian host cell, is integrated into the host cell genome and replicated together with the chromosome(s) into which it has been integrated. Preferably, the "nucleic acid expression vector" may be an expression vector which is usually applied in gene therapeutic methods in humans, particularly a retroviral vector or an adenoviral vector.

The coding sequence of interest may, if necessary, be operably linked to a suitable terminator or to a polyadenylation sequence. In the case of RNA, particularly siRNA, "coding sequence" refers to the sequence encoding or corresponding to the relevant RNA strand or RNA strands.

Further, the vector may comprise a DNA sequence enabling the vector to replicate in the mammalian host cell. Examples of such a sequence – particularly when the host cell is a mammalian cell - is the SV40 origin of replication.

A number of vectors suitable for expression in mammalian cells are known in the art and several of them are commercially available. Some commercially available mammalian expression vectors which may be suitable include, but are not limited to, pMC1neo (Stratagene), pXT1 (Stratagene), pSG5 (Stratagene), pcDNAI (Invitrogen), EBO-pSV2-neo (ATCC 37593), pBPV-1(8-2) (ATCC 37110), pSV2-dhfr (ATCC 37146). Preferred are all suitable gene therapeutic vectors known in the art.

In a particularly preferred embodiment of the invention the vector is a retroviral vector. Retroviruses are RNA-viruses possessing a genome that after the infection of a cell, such as a human cell, is reversely transcribed in DNA and subsequently is integrated into the genome of the host cell. Retroviruses enter their host cell by receptor-mediated endocytosis. After the endocytosis into the cell the expression of the retroviral vector may be silenced to ensure that only a single cell is infected. The integration of the viral DNA into the genome is mediated by a virus-encoded protein called integrase, wherein the integration locus is not defined. Retroviral vectors are particularly appropriate for their use in gene therapeutic methods, since their transfer by receptor-mediated endocytosis into the host cell, also known to those skilled in the art as "retroviral transduction" is particularly efficient. A person skilled in the art also knows how to introduce such retroviral vectors into the host cell using so called "packaging cells".

In another particularly preferred embodiment of the invention, the vector is an adenoviral vector or a derivative thereof. Adenoviral vectors comprise both replication-capable and and replication-deficient vectors. The latter include vectors deficient in the E1 gene.

The recombinant vector is preferably introduced into the mammalian host cells by a suitable pharmaceutical carrier that allows transformation or transfection of the mammalian, in particular human cells. Preferred transformation/transfection techniques include, but are not limited to liposome-mediated transfection, virus-mediated transfection and calcium phosphate transfection.

In a preferred embodiment, the invention relates to the use of a vector system capable of producing siRNAs as defined above, wherein the nucleic acid corresponding to the siRNA is contained in at least one nucleic acid expression vector comprising a first expression cassette containing the nucleic acid corresponding to the sense-RNA-strand under the control of a first promoter and a second expression cassette containing the nucleic acid corresponding to the antisense-RNA-strand under the control of a second promoter.

In the above mentioned vector system, the vector comprises two individual promoters, wherein the first promoter controls the transcription of the sense-strand and the second promoter controls the transcription of the antisense strand (also described in Tuschl, Nature

Biotechnology, Vol. 20, pp. 446-448). Finally the siRNA duplex is constituted by the hybridisation of the first and the second RNA-strand.

The term "expression cassette" is defined herein to include all components which are necessary or advantageous for the expression of a specific target polypeptide. An "expression cassette" may include, but is not limited to, the nucleic acid sequence of interest itself (e.g. encoding or corresponding to the siRNA or polypeptide of interest) and "control sequences". These "control sequences" may include, but are not limited to, a promoter that is operatively linked to the nucleic acid sequence of interest, a ribosome binding site, translation initiation and termination signals and, optionally, a repressor gene or various activator genes. Control sequences are referred to as "homologous", if they are naturally linked to the nucleic acid sequence of interest and referred to as "heterologous" if this is not the case. The term "operably linked" indicates that the sequences are arranged so that they function in concert for their intended purpose, i.e. expression of the desired protein, or, in case of RNA, transcription of the desired RNA.

The promoter used in the aforementioned "expression cassettes" may be any DNA sequence which shows transcriptional activity in a host cell of choice, preferably in a mammalian host cell, particularly in a human host cell. The promoter may be derived from genes encoding proteins either homologous or heterologous to the host cell.

As a promoter in general every promoter known in the prior art can be used that allows the expression of the gene of interest under appropriate conditions in a mammalian host cell, in particular in a human host cell. Particularly promoters derived from RNA polymerase III transcription units, which normally encode the small nuclear RNAs (snRNAs) U6 or the human RNAse P RNA H1, can be used as promoters to express the therapeutic siRNAs. These particularly preferred promoters U6 and H1 RNA which are members of the type III class of Polymerase III promoters are - with the exception of the first transcribed nucleotide (+1 position) - only located upstream of the transcribed region.

In a preferred embodiment, the invention relates to the use of a vector system capable of producing siRNAs for the above identified nucleic acid sequences, wherein the sequence is contained in at least one nucleic acid expression vector comprising an expression cassette containing the sequence of the sense-RNA-strand and of the antisense-RNA-strand under the control of a promoter leading to a single-stranded RNA-molecule and wherein the single-stranded RNA-molecule is capable of forming a back-folded stem-loop-structure.

In this vector system (also described in Tuschl, Nature Biotechnology, Vol. 20, pp. 446-448), only a single RNA-strand is produced under the control of a single promoter, wherein the RNA strand comprises both the sense- and of the antisense-strand of the final double-stranded siRNA molecule. This structure leads to a back-folding of the RNA-strand by hybridisation of the complementary sense- and antisense-sequences under stem-loop formation. Finally the intracellular processing of this fold-back stem-loop-structure gives rise to siRNA.

In another preferred embodiment according to the present invention, the "nucleic acid expression vector" comprises an expression cassette containing the sequence of the sense-RNA-strand and of the antisense-RNA-strand both under the control of a single promoter leading to a single-stranded RNA-molecule. This single-stranded RNA-molecule is hereby capable to form a back-folded stem-loop-structure. These expressed "hairpin RNA-molecules" subsequently give rise to siRNAs after intracellular processing.

In a preferred embodiment of the invention the nucleic acid expression vector that gives rise to the expression of siRNAs according to the present invention is first introduced into therapeutic, non-toxic virus particles or virus-derived particles that are suitable for gene therapeutic applications and that can infect mammalian, in particular human target cells, such as packaging cells etc..

In a preferred embodiment, the first and the second RNA strand of the siRNA may have, independently from the other, a length of 19 to 25 nucleotides, more preferred of 20 to 25 nucleotides, and most preferred of 20 to 22 nucleotides.

In another preferred embodiment, the first and the second RNA strand of the siRNA may have, independently from the other, a length of 26 to 30 nucleotides, more preferred of 26 to 28 nucleotides, and most preferred of 27 nucleotides.

The present invention also relates to the use of and/or methods involving proteins, polypeptides and peptides encoded by the above defined sequences.

In another aspect, the invention relates to the use of isolated proteins or polypeptides comprising a sequence of the group selected of:

(a) a sequence as disclosed in SEQ ID NO. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60;

(b) a sequence that exhibits a sequence identity with any of the sequences according to (a) of at least 25 % over 100 residues,

(c) or fragments of the sequences defined in (a) or (b),

for the manufacture of a medicament for the inhibition of spindle formation or microtubule function during cell division.

Proteins, polypeptides and peptides can be introduced into the cells by various methods known in the art. For example, amphiphilic molecules may be membrane permeable and can enter cells directly. Membrane-bound proteins or polypeptides (usually lipophilic molecules or containing transmembrane domains) may insert directly into cell membranes and can thus exert their biological function. Other ways of introduction or intracellular uptake include microinjection, lipofection, receptor-mediated endocytosis, or the use of suitable carrier-molecules, particularly carrier-peptides. Suitable carrier-peptides include or can be derived from HIV-tat, antennapedia-related peptides (penetratins), galparan (transportan), polyarginine-containing peptides or polypeptides, Pep-1, herpes simplex virus VP-22 protein. Another possible introduction method is to introduce nucleic acid vectors capable of expressing such proteins, polypeptides or peptides

Suitable methods to produce isolated polypeptides are known in the art. For example, such a method may comprise transferring the expression vector with an operably linked nucleic acid molecule encoding the polypeptide into a suitable host cell, cultivating said host cells

under conditions which will permit the expression of said polypeptide or fragment thereof and, optionally, secretion of the expressed polypeptide into the culture medium. Depending on the cell-type different desired modifications, e.g. glycosylation, can be achieved.

The proteins, polypeptides and peptides may also be produced synthetically, e.g. by solid phase synthesis (Merrifield synthesis).

The polypeptides used in the invention may also include fusion polypeptides. In such fusion polypeptides another polypeptide may be fused at the N-terminus or the C-terminus of the polypeptide of interest or fragment thereof. A fusion polypeptide is produced by fusing a nucleic acid sequence (or a portion thereof) encoding another polypeptide to a nucleic acid sequence (or a portion thereof) of the present invention. Techniques for producing fusion polypeptides are known in the art and include ligating the coding sequences so that they are in frame and the expression of the fusion polypeptide is under control of the same promotor(s) and terminator.

Expression of the polypeptides of interest may also be performed using in vitro produced synthetic mRNA. Synthetic mRNA can be efficiently translated in various cell-free systems, including but not limited to, wheat germ extracts and reticulocyte extracts, as well as efficiently translated in cell based systems including, but not limited to, microinjection into frog oocytes, preferably Xenopus laevis oocytes.

Inhibition of spindle formation or microtubule function during cell division using said isolated proteins or polypeptides can be achieved by different ways familiar to the person skilled in the art: Overexpression of the protein or polypeptide may lead to suppression of the endogenous protein's biological function. By introducing deletions or other mutations, or by using suitable fragments, it is possible to generate sequences encoding dominant-negative peptides or polypeptides. Such dominant-negative peptides or polypeptides can inhibit the function of the corresponding endogenous protein. For example, fragments or mutants can be generated which consist only of binding domains but are enzymatically inactive (i.e. partially lacking their biological function). Such dominant-negative molecules may interfere with the biological function of the endogenous proteins or polypeptides by

binding to intracellular binding partners and thus blocking activation of the endogenous molecule.

In another aspect, the invention relates to the use of an antibody which is directed against at least one polypeptide comprising a sequence as defined above for the manufacture of a medicament for the inhibition of spindle formation or microtubule function during cell division.

The term "antibody" as used herein includes both polyclonal and monoclonal antibodies, as well as fragments thereof, such as Fv, Fab and $F(ab)_2$ fragments that are capable of binding antigen or hapten. The present invention also contemplates "humanized" hybrid antibodies wherein amino acid sequences of a non-human donor antibody exhibiting a desired antigen-specificity are combined with sequences of a human acceptor antibody. The donor sequences will usually include at least the antigen-binding amino acid residues of the donor but may comprise other structurally and/or functionally relevant amino acid residues of the donor antibody as well. Such hybrids can be prepared by several methods well known in the art.

Specifically, said antibodies or suitable fragments thereof, particularly in humanized form, may be used as therapeutic agents in a method for treating cancer and other proliferative diseases.

The use of said antibodies may also include the therapeutical inhibition of the above identified nucleic acid molecules or their corresponding polypeptides. In particular, this use may be directed to a proliferative disease.

The antibodies or fragments may be introduced into the body by any method known in the art. Delivery of antibodies, particularly of fragments, into live cells may be performed as described for peptides, polypeptides and proteins. If the antigen is extracellular or an extracellular domain, the antibody may exert its function by binding to this domain, without need for intracellular delivery.

Antibodies can be coupled covalently to a detectable label, such as a radiolabel, enzyme label, luminescent label, fluorescent label or the like, using linker technology established for this purpose. Labeling is particularly useful for diagnostic purposes (see below) or for monitoring the distribution of the antibody within the body or a neoplastic tumor, e.g. by computed tomography, PET (positron emission tomography), or SPECT (single photon emission computed tomography).

In another embodiment, the invention relates to the use of nucleic acid molecules, peptides, polypeptides, proteins, or antibodies, as defined above, for the manufacture of a medicament for the treatment or therapy of a proliferative disease.

In a preferred embodiment, the disease is coronary restenosis or a neoplastic disease, the latter preferably selected from the group consisting of lymphoma, lung cancer, colon cancer, ovarian cancer and breast cancer (see above).

"Proliferative diseases" according to the present invention are diseases associated with excessive cell division or proliferation as for example cancer. Preferably, the proliferative disease is restenosis, particularly coronary restenois, or a neoplastic disease, the latter preferably selected from the group consisting of lymphoma, lung cancer, colon cancer, ovarian cancer and breast cancer.

Restenosis is a re-narrowing of a blood vessel due to growth of tissue at the site of angioplasty or stent implantation. Stents are tiny metal tubes to hold the previously blocked arteries open. However, restenosis still develops in many patients with implanted stents, thus necessitating second angioplasty, stent implantation or even coronary bypass surgery.

Neoplastic diseases are diseases caused by newly forming tissue or cells. In the context of the present invention, the most relevant neoplastic diseases are neoplastic tumors, particularly selected from the group consisting of lymphoma, lung cancer, colon cancer, ovarian cancer and breast cancer.

In another aspect, the invention relates to the use of an isolated nucleic acid molecule comprising a nucleic acid with a sequence selected from the group of sequences consisting of:

a) the nucleic acid sequences presented in SEQ ID NO. 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59;
b) nucleic acid sequences encoding polypeptides that exhibit a sequence identity with the protein encoded by a nucleic acid according to a) of at least 25 % over 100 residues and/or which are detectable in a computer aided search using the BLAST sequence analysis programs with an e-value of at most 10^{-5},
c) sequences of nucleic acid molecules which are capable of hybridizing with the nucleic acid molecules with sequences corresponding to (a) or (b) under conditions of medium or high stringency,
d) the antisense-sequence of any of the sequences as defined in (a), (b) or (c),
e) fragments of (a), (b), (c) or (d),
f) RNA sequences corresponding to any of the sequences as defined in (a), (b), (c), (d), or (e),

for the manufacture of a medicament for the activation of spindle formation or microtubule function during cell division.

In another aspect, the invention relates to the use of a an isolated peptide or polypeptide comprising a peptide or polypeptide with a sequence selected from the group consisting of:

(a) a sequence as disclosed in SEQ ID NO. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60;
(b) a sequence that exhibits a sequence identity with any of the sequences according to (a) of at least 25 % over 100 residues,
(c) fragments of the sequences defined in (a) or (b),

for the manufacture of a medicament for the activation of spindle formation or microtubule function during cell division.

In another aspect, the invention relates to the use of an antibody which is directed against at least one peptide or polypeptide with a sequence as defined above for the manufacture of a medicament for the activation of spindle formation or microtubule function during cell division.

Thus, another use or method involving the above identified nucleic acid sequences, peptides, polypeptides, proteins, and antibodies is directed towards the treatment of a disease in which spindle formation or microtubule function during cell division, is abnormal, deficient or negatively affected.

Diseases with abnormal, deficient or negatively affected spindle formation or microtubule function during cell division may be characterized by increased apoptosis and developmental disorders, in particular growth retardation, or slowed wound healing.

Therefore, a preferred embodiment of the present invention relates to a use or method of the treatment of a disease, wherein the disease is characterized by increased apoptosis, growth retardation, or slowed wound healing.

"Activation of spindle formation or microtubule function during cell division" includes both initiation and stimulation of spindle formation or microtubule function during cell division.

The use may include, but is not limited to, the use of said nucleic acid molecules and their corresponding polypeptides for direct or indirect activation of the expression of said target genes and/or for activation of the function of said target genes. In particular, the use may include the replacement for or the complementation of a lack of function or activity of an endogenous gene involved in spindle formation or microtubule function during cell division.

Expression of RNA or polypeptides may be achieved by introduction of genomic DNA or cDNA containing suitable promoters, preferably constitutive or homologous promoters. Alternatively, any suitable nucleic acid expression vector can be used (see also above). The encoded protein or polypeptide may be full-length or a fragment or peptide with a similar biological function in spindle formation or microtubule function during cell division, particularly with the capability to activate spindle formation or microtubule function during cell division.

All gene therapy techniques known in the art can be used to introduce the sequences into cells or tissues of a subject suffering from a disease negatively affecting spindle formation or microtubule function during cell division. Particularly useful for introduction of the above identified sequences are viral vectors, e.g. retroviral or adenoviral vectors, lipofection and electroporation.

The proteins, polypeptides or peptides may also be generated by any known in vivo or in vitro method and introduced directly into the cells (see above).

It is known that suitable antibodies can be used to activate the biological function of target proteins they bind to. Activation may occur by inducing conformational changes upon binding to the target protein. Another possibility is that the antibody binds two or more target proteins and brings them into sufficiently close physical proximity to induce interaction of the target proteins. The latter mode of activation is particularly known for membrane-bound dimeric receptors.

With respect to the specific embodiments relating to the used nucleic acids, peptides, polypeptides, proteins, and antibodies the same applies as defined above for the other uses of the invention.

In another embodiment, the invention relates to a medicament containing an isolated nucleic acid molecule, peptide, polypeptide, or antibody selected from the group consisting of

a) nucleic acid molecules or nucleic acid expression vectors as defined above,
b) a peptide or polypeptide comprising a sequence as defined above,
c) an antibody directed against at least one peptide or polypeptide according to (b).

Preferably this isolated nucleic acid molecule is an RNA molecule and preferably is double-stranded. Particularly the isolated nucleic acid molecule is an siRNA molecule according to the present invention.

The medicaments may be used or applied in methods for the therapy of any kind of proliferative disease, such as cancer, preferably for the therapy of diseases in which spindle formation or microtubule function during cell division play a role, particularly for the therapy of a lymphoma, lung cancer, colon cancer, ovarian cancer or breast cancer.

The medicaments may also be used or applied in methods for the therapy of any kind of disease associated with abnormal or deficient spindle formation or microtubule function during cell division, particularly diseases characterized by increased apoptosis, developmental disorders or abnormalities (particularly growth retardation) and slowed wound healing.

The following considerations for medicaments and their administration apply also to the medicaments of the invention as to the above disclosed uses.

The medicament preferably comprises additionally a suitable pharmaceutically acceptable carrier, preferably virus-particles or virus-derived particles that may harbour the viral vectors, transfection solutions comprising liposomes, particularly cationic liposomes, calcium phosphate etc. Preferably a carrier is used, which is capable of increasing the efficacy of the expression vector or virus particles containing the expression vector to enter the mammalian target cells. The medicament may additionally comprise other carrier

substances, preferably starch, lactose, fats, stearin acid, alcohol, physiological NaCl-solutions or further additives, in particular stabilizers, preservatives, dyes and flavourings.

The medicaments may also comprise other suitable substances. For example, RNA or siRNA containing medicaments may contain substances which stabilize double-stranded RNA molecule and/or which enable the double-stranded RNA molecule or DNA expression vector to be transfected or to be injected into the human or animal cell.

Administration can be carried out by known methods, wherein a nucleic acid is introduced into a desired cell in vitro or in vivo. For therapeutic applications, the medicament may be in form of a solution, in particular an injectable solution, a cream, ointment, tablet, suspension, granulate or the like. The medicament may be administered in any suitable way, in particular by injection, by oral, nasal, rectal application. The medicament may particularly be administered parenteral, that means without entering the digestion apparatus, for example by subcutaneous injection. The medicament may also be injected intravenously in the form of solutions for infusions or injections. Other suitable administration forms may be direct administrations on the skin in the form of creams, ointments, sprays and other transdermal therapeutic substances or in the form of inhalative substances, such as nose sprays, aerosoles or in the form of microcapsules or implantates.

The optimal administration form and/or administration dosis for a medicament either comprising double-stranded RNA molecules with the above sequences or comprising nucleic acid vectors capable to express such double-stranded RNA molecules depend on the type and the progression of the disease to be treated.

Preferably, the activator or inhibitor is administered in pharmaceutically effective amount. As used herein, a "pharmaceutically effective amount" of an activator or inhibitor is an amount effective to achieve the desired physiological result, either in cells treated *in vitro* or in a subject treated *in vivo*. Specifically, a pharmaceutically effective amount is an amount sufficient to positively influence, for some period of time, one or more clinically defined pathological effects associated with proliferative diseases or diseases associated

with abnormal, deficient or negatively affected spindle formation or microtubule function during cell division. The pharmaceutically effective amount may vary depending on the specific activator or inhibitor selected, and is also dependent on a variety of factors and conditions related to the subject to be treated and the severity of the disease. For example, if the activator or inhibitor is to be administered *in vivo*, factors such as age, weight, sex, and general health of the patient as well as dose response curves and toxicity data obtained in pre-clinical animal tests would be among the factors to be considered. If the activator or inhibitor is to be contacted with cells *in vitro*, one would also design a variety of pre-clinical *in vitro* studies to assess parameters like uptake, half-life, dose, toxicity etc. The determination of a pharmaceutically effective amount for a given agent (activator or inhibitor) is well within the ability of those skilled in the art. Preferably, the activator or inhibitor is present in a concentration of 0,1 to 50% per weight of the pharmaceutical composition, more preferably 10 to 30%.

An inhibitor, activator, or drug according to the present invention may also be a "small molecule". Small molecules are molecules which are not proteins, peptides antibodies or nucleic acids, and which exhibit a molecular weight of less than 5000 Da, preferably less than 2000 Da, more preferably less than 2000 Da, most preferably less than 500 Da. Such small molecules may be identified in high throughput procedures/screening assays starting from libraries. Such methods are known in the art. Suitable small molecules can also be designed or further modified by methods known as combinatorial chemistry.

The genes/proteins that are provided by the current application and that possess one of the sequences as defined in (a) to (f), can be used in a high-throughput or other screen for new agents that inhibit or activate spindle formation or microtubule function during cell division. Particularly inhibitors of spindle formation or microtubule function during cell division identified by such a screen may be used as medicaments for the therapy of proliferative diseases, particularly for the therapy of a disease in which spindle formation or microtubule function during cell division play a role.

In another aspect, the present invention relates to the use of an isolated nucleic acid molecule comprising a sequence as defined above or the use of a ligand binding specifically at least one polypeptide comprising a sequence as defined above for the in

vitro diagnosis of a proliferative disease or a disease associated with abnormal spindle formation or microtubule function during cell division.

In a preferred embodiment, diagnosis relates to proliferative diseases as defined above.

In another preferred embodiment, diagnosis relates to diseases associated with abnormal, deficient or negatively affected spindle formation or microtubule function during cell division, as they are described above. Diseases with "abnormal" spindle formation or microtubule function during cell division include diseases in which spindle formation or microtubule function during cell division is deficient or negatively affected.

In a proliferative disease, expression of endogenous genes corresponding to the above identified sequences may be increased.

In a disease in which spindle formation or microtubule function during cell division are abnormal, deficient or negatively affected, expression of the corresponding endogenous genes may be lowered. Furthermore, the corresponding endogenous gene may be mutated, rendering the corresponding protein less active or non-functional.

The diagnostic use of the above identified nucleic acid molecules and probes may include, but is not limited to the quantitative detection of expression of said target genes in biological probes (preferably, but not limited to tissue samples, cell extracts, body fluids, etc.), particularly by quantitative hybridization to the endogenous nucleic acid molecules comprising the above-characterized nucleic acid sequences (particularly cDNA, RNA)

Expression of the endogenous genes or their corresponding proteins can be analyzed in vitro in tissue samples, body fluids, and tissue and cell extracts. Expression analyis can be performed by any method known in the art, such as RNA in situ hybridization, PCR (including quantitative RT-PCR), and various serological or immunological assays which include, but are not limited to, precipitation, passive agglutination, enzyme-linked immunosorbent antibody (ELISA) technique and radioimmunoassay techniques.

The diagnostic use may also include the detection of mutations in endogenous genes corresponding to the above identified nucleic acid sequences.

Suitable nucleic acid probes may be synthesized by use of DNA synthesizers according to standard procedures or, preferably for long sequences, by use of PCR technology with a selected template sequence and selected primers. The probes may be labeled with any suitable label known to those skilled in the art, including radioactive and non-radioactive labels. Typical radioactive labels include ^{32}P, ^{125}I, ^{35}S, or the like. A probe labeled with a radioactive isotope can be constructed from a DNA template by a conventional nick translation reaction using a DNase and DNA polymerase. Non-radioactive labels include, for example, ligands such as biotin or thyroxin, or various luminescent or fluorescent compounds. The probe may also be labeled at both ends with different types of labels, for example with an isotopic label at one end and a biotin label at the other end. The labeled probe and sample can then be combined in a hybridization buffer solution and held at an appropriate temperature until annealing occurs. Such nucleic acid probes may also be used for other than diagnostic purposes, e.g. for the identification of further homologs or orthologs.

"Ligands" binding specifically to said polypeptides are known in the art. Such ligands include proteins or polypeptides, for example intracellular binding partners, antibodies, molecular affinity bodies, and small molecules. Specifically binding ligands can be identified by standard screening assays known in the art (see also below), for example by yeast two-hybrid screens and affinity chromatography. A specifically binding ligand does not need to exert another function such as inhibiting or acitvating the molecule with which it interacts.

In a preferred embodiment, the ligand is an antibody binding specifically at least one polypeptide comprising a sequence as defined above.

"Specific binding" according to the present invention means that the polypeptide to be identified (the target polypeptide) is bound with higher affinity than any other polypeptides present in the sample. Preferred is at least 3 times higher affinity, more preferred at least 10 times higher affinity, and most preferred at least 50 times higher affinity. Non-specific

binding ("cross-reactivity") may be tolerable if the target polypeptide can be identified unequivocally, e.g. by its size on a Western blot.

Preferably the specifically binding ligands can be labeled, e.g. with fluorescent labels, enzymes, molecular tags (e.g. GST, myc-tag or the like), radioactive isotopes, or with labeled substances, e.g. labeled secondary antibodies. For MRI (magnetic resonance imaging), the ligands may be chelated with gadolinium, superparamagnetic iron oxide or lanthanides. For PET (positron emission tomography) or SPECT (single photon emission computed tomography) commonly used isotopes include ^{11}C, ^{18}F, ^{15}O, ^{13}N, ^{86}Y, ^{90}Y, and ^{16}Co.

In another aspect, the present invention relates to a diagnostic kit containing an isolated nucleic acid molecule as defined above and/or a ligand which is directed against at least one polypeptide as defined above for the in vitro diagnosis of a proliferative disease or a disease associated with abnormal spindle formation or microtubule function during cell division.

Diagnostic kits may comprise suitable isolated nucleic acid or amino acid sequences of the above identified genes or gene products, labelled or unlabelled, and/or specifically binding ligands (e.g. antibodies) thereto and auxiliary reagents as appropriate and known in the art. The assays may be liquid phase assays as well as solid phase assays (i.e. with one or more reagents immobilized on a support). The diagnostic kits may also include ligands directed towards other molecules indicative of the disease to be diagnosed.

In another aspect, the invention relates to the use of an isolated nucleic acid molecule or a nucleic acid expression vectors as defined above or of an antibody which is directed against at least one polypeptide comprising a sequence as defined above, in a screening assay for the identification and characterization of drugs that inhibit or activate spindle formation or microtubule function during cell division.

In another aspect, the invention relates to the use of a peptide, polypeptide or protein with a sequence as defined above in a screening assay for interacting drugs, that inhibit or activate

spindle formation or microtubule function during cell division. Such interacting molecules may also be used as ligands for diagnosis as described above.

"Screening assay" according to the present invention relates to assays which allow to identify substances, particularly potential drugs, that inhibit or activate spindle formation or microtubule function during cell division, by screening libraries of substances. "Screening assay" according to the present invention also relates to assays to screen libraries for substances capable of binding to the nucleic acids, polypeptides, peptides or antibodies defined above. Suitable libraries may, for example, include small molecules, peptides, polypeptides or antibodies.

The invention relates to assays for identification as well as to assays for characterization of substances that inhibit or activate spindle formation or microtubule function during cell division or that bind to said nucleic acids, polypeptides, peptides or antibodies. Particularly, the invention relates to screening assays for drugs. Such drugs may be identified and characterized from libraries of unspecified compounds as well as libraries of drugs which are already known for treatment of other diseases. For such known drugs also potential side-effects and therapeutically applicable doses are known.

Suitable drugs include "interacting drugs", i.e. drugs that bind to the polypeptides or nucleic acids identified above. Such interacting drugs may either inhibit or activate the molecule they are bound to. Examples for interacting substances are peptide nucleic acids comprising sequences identified above, antisense RNAs, siRNAs, ribozymes, aptamers, antibodies and molecular affinity bodies (CatchMabs, Netherlands). Such drugs may be used according to any aspect of the present invention, including use for the manufacture of medicaments and methods of treatment of proliferative diseases. It is known that such interacting drugs can also be labeled and used as ligands for diagnosis of a disease associated with spindle formation or microtubule function during cell division.

Suitable screening assays are known in the art. For example, in a preferred embodiment of the invention the screening method for the identification and characterization of an inhibitor or an activator molecule that inhibits or activates spindle formation or microtubule function during cell division comprises the following steps:

a) transformation of a nucleic acid molecule or a nucleic acid expression vector as defined above into a host cell or host organism,

b) cultivation of the host cell or host organism obtained in step a) under conditions that allow the overexpression of the polypeptide or RNA encoded by or corresponding to the nucleic acid of step (a) either in the presence or in the absence of at least one candidate for an inhibitor- or activator-molecule, and

c) analysis of the spindle formation or microtubule function during cell division in the cultivated cell or organism and thereby identification of an inhibitor or activator of spindle formation or microtubule function during cell division.

The term "expression vector" as used herein does not only relate to RNA or siRNA expressing vectors, but also to vectors expressing peptides, polypeptides or proteins.

The transfer of the expression vector into the host cell or host organism hereby may be performed by all known transformation or transfection techniques, including, but not limited to calcium phosphate transformation, lipofection, microinjection. Host cell/host organisms may be all suitable cells or organisms that allow detection of impaired cell division, preferably of impaired spindle formation or microtubule function during cell division. A particularly preferred host organism is C. elegans, since its translucent body allows an easy detection of failures during cell division, including spindle formation or microtubule function during cell division. Vertebrate cells, preferably mammalian, more preferably human cells, in particular human cell lines are also preferred host cells. The expression vector may be any known vector that is suitable to allow the expression of the nucleic acid sequence as defined above. Preferred expression vectors possess expression cassettes comprising a promoter that allows an overexpression of the RNA, peptide or polypeptide as defined above.

After the transfer of the expression vector into the host cell/host organism one part of the host cells or host organisms are cultured in the presence of at least one candidate of an inhibitor- or activator-molecule and under culture conditions that allow the expression, preferably the overexpression of the RNA, peptide or polypeptide as defined above. The

other part of the transfected host cells are cultured under the same culture conditions, but in the absence of the candidate of an inhibitor- or activator-molecule.

Finally, after an appropriate incubation time/culture period the proliferation state and/or cell divisions for host cells or host organisms that had been cultured in the presence or in the absence of the at least one candidate for an inhibitor or an activator molecule are detected or preferably quantified. This detection or quantification step is preferably done by time lapse fluorescence or DIC microscopy, particularly in those cases when the host organism is C. elegans or another mostly translucent organism that is available to be analysed by time lapse fluorescence or DIC microscopy. The detection /quantification step may also be done by any other technique known to the state of the art that is suitable to analyse the proliferation state or the extent of cell division, preferably all kinds of microscopic techniques.

In another preferred embodiment, the screening method for the identification and characterization of an interacting molecule that inhibits or activates spindle formation or microtubule function during cell division from a library of test substances comprises the following steps:

a) recombinantly expressing a polypeptide encoded by a nucleic acid molecule sequence as defined above in a host cell,

b) isolating and optionally purifying the recombinantly expressed polypeptide of step (a),

c) optionally labelling of the test substances and/or labelling of the recombinantly expressed polypeptide,

d) immobilizing the recombinantly expressed polypeptide to a solid phase,

e) contacting of at least one test substance with the immobilized polypeptide,

f) optionally one or more washing steps,

g) detecting the binding of the at least one test substance to the immobilized polypeptid at the solid phase, and

h) performing a functional assay for inhibition or activation of spindle formation or microtubule function during cell division.

Step a) includes the recombinant expression of the above identified polypeptide or of its derivative from a suitable expression system, in particular from cell-free translation, bacterial expression, or baculuvirus-based expression in insect cells.

Step b) comprises the isolation and optionally the subsequent purification of said recombinantly expressed polypeptides with appropriate biochemical techniques that are familiar to a person skilled in the art.

Alternatively, these screening assays may also include the expression of derivatives of the above identified polypeptides which comprises the expression of said polypeptides as a fusion protein or as a modified protein, in particular as a protein bearing a "tag"-sequence. These "tag"-sequences consist of short nucleotide sequences that are ligated 'in frame' either to the N- or to the C-terminal end of the coding region of said target gene. Commonly used tags to label recombinantly expressed genes are the poly-Histidine-tag which encodes a homopolypeptide consisting merely of histidines, particularly six or more histidines, GST (glutathion S-transferase), c-myc, FLAG®, MBP (maltose binding protein), and GFP. In this context the term "polypeptide" does not merely comprise polypeptides with the nucleic acid sequences of SEQ ID No. 1 to 59, their naturally occuring homologs, preferably orthologs, more preferably human orthologs, but also derivatives of these polypeptides, in particular fusion proteins or polypeptides comprising a tag-sequence.

These polypeptides, particularly those labelled by an appropriate tag-sequence (for instance a His-tag or GST-tag), may be purified by standard affinity chromatography protocols, in particular by using chromatography resins linked to anti-His-tag-antibodies or to anti-GST-antibodies which are both commercially available. Alternatively, His-tagged molecules may be purified by metal chelate affinity chromatography using Ni-ions. Alternatively to the use of 'label-specific' antibodies the purification may also involve the

use of antibodies against said polypeptides. Screening assays that involve a purification step of the recombinantly expressed target genes as described above (step 2) are preferred embodiments of this aspect of the invention.

In an - optional - step c) the compounds tested for interaction may be labelled by incorporation of radioactive isotopes or by reaction with luminescent or fluorescent compounds. Alternatively or additionally also the recombinantly expressed polypeptide may be labelled.

In step d) the recombinantly expressed polypeptide is immobilized to a solid phase, particularly (but not limited) to a chromatography resin. The coupling to the solid phase is thereby preferably established by the generation of covalent bonds.

In step e) a candidate chemical compound that might be a potential interaction partner of the said recombinant polypeptide or a complex variety thereof (particularly a drug library) is brought into contact with the immobilized polypeptide.

In an - optional – step f) one or several washing steps may be performed. As a result just compounds that strongly interact with the immobilized polypeptide remain bound to the solid (immobilized) phase.

In step g) the interaction between the polypeptide and the specific compound is detected, in particular by monitoring the amount of label remaining associated with the solid phase over background levels.

Such interacting molecules may be used without functional characterization for diagnostic purposes as described above.

In step h) the interacting molecule is further analyzed for inhibition or activation of spindle formation or microtubule function during cell division. Such analysis or functional assay can be performed according to any assay system known in the art. A suitable assay may include the cultivation of a host cell or host organism in the presence (test condition) or absence (control condition) of the interacting molecule, and comparison of spindle formation or microtubule function during cell division under test and control conditions.

In another aspect, the invention relates to a method for the preparation of a pharmaceutical composition wherein an inhibitor or activator of spindle formation or microtubule function during cell division is identified according to any of the screening methods described above, synthesized in adequate amounts and formulated into a pharmaceutical composition.

Suitable methods to synthesize said inhibitor or activator molecules are known in the art. For example, peptides or polypeptides can be synthesized by recombinant expression (see also above), antibodies can be obtained from hybridoma cell lines or immunized animals. Small molecules can be synthesized according to any known organic synthesis methods.

Adequate amounts relate to pharmaceutically effective amounts.

Similarly, the inhibitor or activator may be provided by any of the screening methods described above and formulated into a pharmaceutical composition.

Brief Description of the Drawings

Fig. 1 shows DIC microscopy images taken from time-lapse recording of the first round of cell division in C. elegans F1 progeny from F0 an parent treated with dsRNA (RNAi) directed against C13F10.2.

Fig. 2 shows an amino acid sequence alignment of C13F10.2 and the corresponding Drosophila and human ortholog.

Fig. 3 shows DIC microscopy images taken from time-lapse recording of the first round of cell division in C. elegans F1 progeny from F0 a parent treated with dsRNA (RNAi) directed against C25A1.9.

Fig. 4 shows an amino acid sequence alignment of C25A1.9 and the corresponding human ortholog.

Fig. 5 shows DIC microscopy images taken from time-lapse recording of the first round of cell division in C. elegans F1 progeny from F0 a parent treated with dsRNA (RNAi) directed against F54B3.3.

Fig. 6 shows an amino acid sequence alignment of F54B3.3 and its corresponding Drosophila and human orthologs and mouse homolog.

Fig. 7 shows DIC microscopy images taken from time-lapse recording of the first round of cell division in C. elegans F1 progeny from F0 a parent treated with dsRNA (RNAi) directed against F08B6.2.

Fig. 8 shows an amino acid sequence alignment of F08B6.2 and its corresponding Drosphila and human orthologs.

Fig. 9 shows DIC microscopy images taken from time-lapse recording of the first round of cell division in C. elegans F1 progeny from F0 a parent treated with dsRNA (RNAi) directed against CD4.4.

Fig. 10 shows an amino acid sequence alignment of CD4.4 and its corresponding Drosophila and human orthologs.

Fig. 11 shows DIC microscopy images taken from time-lapse recording of the first two rounds of cell division in C. elegans F1 progeny from F0 a parent treated with dsRNA (RNAi) directed against ZK546.1.

Fig. 12 shows an amino acid sequence alignment of ZK546.1, its corresponding human ortholog and its Drosophila and mouse homologs.

Fig. 13 shows DIC microscopy images taken from time-lapse recording of the first two rounds of cell division in C. elegans F1 progeny from F0 a parent treated with dsRNA (RNAi) directed against C56C10.3.

Fig. 14 shows an amino acid sequence alignment of C56C10.3 and its corresponding human, mouse, and Drosophila orthologs.

Fig. 15 shows DIC microscopy images taken from time-lapse recording of the first two rounds of cell division in wild type untreated C. elegans.

Fig. 16: shows the remaining mRNA levels after RNAi treatment of HeLa cells. RNAi treatment of HeLa cells with siRNAs directed against NP_056972.1, CAD38936, NP_060387.1, NP_076974.1 and NP_060658.1, the human orthologs of C. elegans genes ZK546.1, CD4.4 , C25A1.9 , C13F10.2 and F54B3.3 respectively, results in the specific reduction to mRNA levels below 20% compared to control treated samples for NP_056972.1, CAD38936 and NP_060658.1, and a reduction below 50% for NP_060387.1 and NP_076974.1.
mRNA, remaining mRNA levels (% of negative control treated sample); pos. ctrl., positive control; neg. ctrl., negative control.

Fig. 17: shows the effect of RNAi treatment on cell proliferation, apoptosis, and mitosis in HeLa cells. For graphical presentation, the proliferation, apoptosis rate, and MI of untreated cells were set to 100.
prolif., cell proliferation; apopt., apoptosis; MI, mitotic index; %, percent compared to untreated control; scr. ctrl., scrambled control; untrtd., untreated; n.d., not determined.

The following examples illustrate the present invention without, however, limiting the same thereto.

EXAMPLE 1: Protocol for identifying functional orthologs in other species

To identify orthologous genes, the following procedure was used: The identified homologous amino acid sequences themselves were used for BLAST searches. If the original C. elegans protein was (re-)identified by a BLAST hit with an e-value of less than 10^{-5}, the identified homolog was defined as an ortholog. The BLAST search was performed with the default parameters and the low complexity filter on. An alternative parameter for identification of homologous genes can be the percentage of sequence identity. Over 100 residues, a sequence identity of 30% defines a homologous gene. After the BLAST search is completed, multiple sequence alignment is performed using appropriate software (for example, CLUSTAL W) and a neighbour joining phylogenetic tree is generated. Any person skilled in the art can identify the human ortholog from a

phylogenetic tree. Essentially, the human sequence that is separated on the tree by a single speciation event or most closely related on the tree is likely to be an ortholog.

EXAMPLE 2: Generation of dsRNA molecules for RNAi experiments

First, oligonucleotide primer pair sequences were selected to amplify portions of the gene of interest's coding region using standard PCR techniques. Primer pairs were chosen to yield PCR products containing at least 500 bases of coding sequence, or a maximum of coding bases for genes smaller than 500 bases. In order to permit the subsequent use of the PCR product as a template for *in vitro* RNA transcription reactions from both DNA strands, the T7 polymerase promoter sequence "TAATACGACTCACTATAGG" was added to the 5' end of forward primers, and the T3 polymerase promoter sequence "AATTAACCCTCACTAAAGG" was added to the 5' end of reverse primers. The synthesis of oligonucleotide primers was completed by a commercial supplier (Sigma-Genosys, UK or MWG-Biotech, Germany).

PCR reactions were performed in a volume of 50 µl, with Taq polymerase using 0.8 µM primers and approximately 0.1 µg of wild-type (N2 strain) genomic DNA template. The PCR products were EtOH precipitated, washed with 70% EtOH and resuspended in 7.0 µl TE. 1.0 µl of the PCR reaction was pipetted into each of two fresh tubes for 5 µl transcription reactions using T3 and T7 RNA polymerases. The separate T3 and T7 transcription reactions were performed according to the manufacturer's instructions (Ambion, Megascript kit), each diluted to 50 µl with RNase-free water and then combined. The mixed RNA was purified using RNeasy kits according to the manufacturer's instructions (Qiagen), and eluted into a total of 130 µl of RNase-free H_2O. 50 µl of this was mixed with 10 µl 6X injection buffer (40 mM KPO_4 pH 7.5, 6 mM potassium citrate, pH 7.5, 4% PEG 6000). The RNA was annealed by heating at 68°C for 10 min, and at 37°C for 30 min. Concentration of the final dsRNAs were measured to be in the range of 0.1-0.3 µg/µl. The products of the PCR reaction, of the T3 and T7 transcription reactions, as well as the dsRNA species were run on 1% agarose gels to be examined for quality control

purposes. Success of double stranding was assessed by scoring shift in gel mobility with respect to single stranded RNA, when run on non-denaturing gels.

EXAMPLE 3: Injections of dsRNA and phenotypic assays

dsRNAs were injected bilaterally into the syncytial portion of both gonads of wild-type (N2 strain) young adult hermaphrodites, and the animals incubated at 20°C for 24 hrs. Embryos were then dissected out from the injected animals and analyzed by time-lapse differential interference contrast videomicroscopy for potential defects in cell division processes, capturing 1 image every 5 seconds, as previously described (Gönczy *et al.*, Dissection of cell division processes in the one cell stage *Caenorhabditis elegans* embryo by mutational analysis. *J Cell Biol* 144, 927-946 (1999)). For each experiment, embryos from at least 3 different injected worms were filmed in this manner, from shortly after fertilization until the four cell stage. Embryos from 2 additional injected worms were recorded for shorter periods, covering the 2 cell and the 4 cell stage, respectively, thus yielding documentation for at least 5 injected worms in each experiment.

In some cases, embryos exhibited acute sensitivity to osmotic changes, as evidenced by their loss of structural integrity during the dissection of the injected animals. In order to overcome this limitation, injected animals were not dissected, but rather, anaesthetized for 10 min in M9 medium containing 0.1% tricaine and 0.01% tetramisole, and mounted intact on an agarose pad to observe the F1 embryogenesis *in utero* (Kirby et al., Dev. Biol. 142, 203-215 (1990)). The resolution achieved by viewing through the body wall does not equal that achieved by observing dissected embryos, and only limited phenotypic analysis was conducted in these cases.

Three injected animals were also transferred to a fresh plate 24 hrs after injection of dsRNA, and left at 20°C. Two days later, the plate was checked with a stereomicroscope (20-40x total magnification) for the presence of F1 larvae (L2's-L4's), as well as their developmental stage. Two days after that, the plate was inspected again for the presence of F1 adults, as well as their overall body morphology and the presence of F2 progeny.

EXAMPLE 4: Characterization of the *C. elegans* gene C13F10.2

dsRNA was designed and used to specifically silence the expression of the *C. elegans* gene by RNAi, thereby testing its functional involvement in the first round of embryonic cell division in this metazoan species. The dsRNA was synthesized *in vitro* from PCR-amplified wild type genomic DNA fragments of the C13F10.2 gene. For PCR, the following primer pair was used: "TAATACGACTCACTATAGGGCGGCTCTTTTCTTCCATTT" with "AATTAACCCTCACTAAAGGTTTCATTCGTCTTCCTCGCT" as forward and reverse primers, respectively. The dsRNA was purified, and injected into adult hermaphrodite worms. The phenotypic consequences of the RNAi treatment were documented 24 hours later in the F1 progeny of injected worms, using time-lapse differential interference contrast (DIC) microscopy. Embryo recordings started ~20 minutes after fertilization, while the female pronucleus is completing its meiotic divisions, until the 2 cell stage, ~15 to 20 minutes later.

Control worms were either not injected, or injected with irrelevant dsRNA. Irrelevant dsRNA was made of the same nucleotide composition as the experimental dsRNA, but the nucleotides were in random order. In the F1 progeny of such control worms the cellular events of the first two rounds of embryonic cell division were found to exhibit very limited variability, as observed by DIC microscopy. All processes that were examined and scored for the possibility of phenotypic deviations are listed and illustrated in Figure 13. Briefly, the antero-posterior polarity of the embryo is initially determined by the position of the male pronucleus at the cortex, shortly after entry into the egg. This is accompanied by a clear, coordinated flow of yolk granules through the central portion of the cytoplasm along the embryo's longitudinal axis towards the male pronucleus, and a concomitant series of cortical waves or ruffles progressing towards the anterior of the embryo. Shortly thereafter, the male and female pronuclei undergo highly patterned migrations resulting in their meeting within the posterior half of the embryo, followed by a centration and rotation of the pronuclear pair and associated centrosomes to set up the future mitotic spindle along the embryo's longitudinal axis. After synchronous breakdown of the pronuclear envelopes, the clearly bipolar mitotic spindle is initially short, but then rockingly elongates. These

movements are accompanied by a slight posterior displacement of the posterior spindle pole, while the anterior spindle pole remains approximately stationary. This then results in an asymmetric positioning of the spindle during anaphase and telophase, thereby yielding an asymmetric placement of the cytokinetic furrow, and generating unequally-sized daughter cells: a smaller posterior P1 blastomere, and larger anterior AB blastomere. While the AB nucleus then migrates directly to the center of the AB cell, the P1 nucleus typically migrates further towards the posterior of that cell, before undergoing a pronounced 90° rotation while re-migrating to the anterior P1 cortex with one of its duplicated centrosomes leading. This insures that the P1 blastomere then divides along the embryo's longitudinal axis, perpendicular to that of the AB blastomere. These two divisions occur asynchronously, with P1 lagging 2-3 minutes behind AB.

In the F1 embryos of worms injected with dsRNA, the following highly reproducible phenotypes are observed (Fig. 1). The mitotic spindle (indicated by arrow heads) drifts and bends during elongation, suggesting weakened microtubule-cortex interactions. The phenotype is embryonic lethal.

All observed phenotypes indicate a requirement for C13F10.2 gene function in spindle formation or microtubule function during cell division. Since this function is essential to cell division throughout metazoans, this gene and any homologs and derivatives thereof represent excellent tools for use in the development of a wide range of therapeutics including anti-proliferative agents. Analysis of the C13F10.2 gene sequence reveals clear orthologs in human (GenBank Accession No. NP_076974) and Drosophila (GenBank Accession No. AAF49911) which have no function ascribed to them until now. In particular, there has been no information linking the orthologs to spindle formation or microtubule function during cell division. Based on the extremely high sequence conservation at the protein level, it can be concluded that these genes most likely encode proteins with equivalent function in spindle formation or microtubule function during cell division in humans and Drosophila.

EXAMPLE 5: Characterization of the *C. elegans* gene C25A1.9

dsRNA was designed and used to specifically silence the expression of the *C. elegans* gene by RNAi, thereby testing its functional involvement in the first round of embryonic cell division in this metazoan species. The dsRNA was synthesized *in vitro* from PCR-amplified wild type genomic DNA fragments of the C25A1.9 gene. For PCR, the following primer pair was used: "TAATACGACTCACTATAGGCACTTAATGCGCCCATTTTC" with "AATTAACCCTCACTAAAGGTTAGCGGGACTGCTATTGCT" as forward and reverse primers, respectively. The dsRNA was purified, and injected into adult hermaphrodite worms. The phenotypic consequences of the RNAi treatment were documented 24 hours later in the F1 progeny of injected worms, using time-lapse differential interference contrast (DIC) microscopy. Embryo recordings started ~20 minutes after ferilization, while the female pronucleus is completing its meiotic divisions, until the 2 cell stage, ~15 to 20 minutes later.

In the F1 embryos of worms injected with dsRNA, the following highly reproducible phenotypes are observed (Fig. 3). The pronuclei remain slightly posterior, leading to incomplete pronuclear centration (Fig. 3A, B). The mitotic spindle is hardly visible and spindle positioning lacks the rocking phase (Fig. 3C-E). In some cases, this can result in chromosome segregation defects (Fig. 3F, arrow head indicates an additional karyomere in AB blastomere). The phenotype is embryonic lethal.

All observed phenotypes indicate a requirement for C25A1.9 gene function in spindle formation or microtubule function during cell division. Since this function is essential to cell division throughout metazoans, this gene and any homologs and derivatives thereof represent excellent tools for use in the development of a wide range of therapeutics including anti-proliferative agents. Analysis of the C25A1.9 gene sequence reveals a clear homolog in human (GenBank Accession No. NP_060387) which has had no function ascribed to it until now. In particular, there has been no information linking the homolog to spindle formation or microtubule function during cell division. Based on the extremely high sequence conservation at the protein level, it can be concluded that this gene most likely encodes a protein with equivalent function in spindle formation or microtubule function during cell division in humans.

EXAMPLE 6: Characterization of the *C. elegans* gene F54B3.3

dsRNA was designed and used to specifically silence the expression of the *C. elegans* gene by RNAi, thereby testing its functional involvement in the first round of embryonic cell division in this metazoan species. The dsRNA was synthesized *in vitro* from PCR-amplified wild type genomic DNA fragments of the F54B3.3 gene. For PCR, the following primer pair was used: "TAATACGACTCACTATAGGAGAGGTCGAGAACGAGACCA" with "AATTAACCCTCACTAAAGGATCGAACTGCTCTGGCTGAT" as forward and reverse primers, respectively. The dsRNA was purified, and injected into adult hermaphrodite worms. The phenotypic consequences of the RNAi treatment were documented 24 hours later in the F1 progeny of injected worms, using time-lapse differential interference contrast (DIC) microscopy. Embryo recordings started ~20 minutes after ferilization, while the female pronucleus is completing its meiotic divisions, until the 2 cell stage, ~15 to 20 minutes later.

In the F1 embryos of worms injected with dsRNA, the following highly reproducible phenotypes are observed (Fig. 5). Pronuclei are not centered and a short spindle is set up along the dorso-ventral axis (Fig. 5 A). This results in aberrant cleavage site specification and furrowing at three sites (Fig. 5 B-D, white arrows). Cytokinesis fails, the reforming nuclei stay closely apposed to each other (Fig. 5 D-H, black arrows). An additional karyomere is formed at the posterior (Fig. 5 G-H, white arrow).

All observed phenotypes indicate a requirement for F54B3.3 gene function in spindle formation or microtubule function during cell division. Since this function is essential to cell division throughout metazoans, this gene and any homologs and derivatives thereof represent excellent tools for use in the development of a wide range of therapeutics including anti-proliferative agents. Analysis of the F54B3.3 gene sequence reveals clear orthologs in human (GenBank Accession No. NP_060658) and Drosophila (GenBank Accession No. AAF55289) which have no function ascribed to them until now. Based on sequence analysis, the Drosophila protein has been described as ATPase-related. Additionally, homologs have been identified in mouse (GenBank Accession No.

XP_109399), rat (GenBank Accession No. P46462 or NP_446316), and Saccharomyces cerevisiae (GenBank Accession No. NP_015349). However, there has been no information linking the genes to spindle formation or microtubule function during cell division. Based on the extremely high sequence conservation at the protein level, it can be concluded that these genes, particularly the orthologs, most likely encode proteins with equivalent function in spindle formation or microtubule function during cell division in their respective species.

EXAMPLE 7: Characterization of the *C. elegans* gene F08B6.2

dsRNA was designed and used to specifically silence the expression of the *C. elegans* gene by RNAi, thereby testing its functional involvement in the first round of embryonic cell division in this metazoan species. The dsRNA was synthesized *in vitro* from PCR-amplified wild type genomic DNA fragments of the F08B6.2 gene. For PCR, the following primer pair was used: "TAATACGACTCACTATAGGCTTCACCGAAAGCCAAGAAG" with "AATTAACCCTCACTAAAGGGAGGTTTGAAAGCGATGGTG" as forward and reverse primers, respectively. The dsRNA was purified, and injected into adult hermaphrodite worms. The phenotypic consequences of the RNAi treatment were documented 24 hours later in the F1 progeny of injected worms, using time-lapse differential interference contrast (DIC) microscopy. Embryo recordings started ~20 minutes after ferilization, while the female pronucleus is completing its meiotic divisions, until the 2 cell stage, ~15 to 20 minutes later.

In the F1 embryos of worms injected with dsRNA, the following highly reproducible phenotypes are observed (Fig. 7). Pronuclear centration and rotation are inaccurate. The rocking phase of the mitotic spindle is less coordinated than normal (Fig. 7 A-D, arrows). Rotation of the P1 nucleus is jerky (Fig. 7 E-F, arrows). The phenotype is embryonic lethal.

All observed phenotypes indicate a requirement for F08B6.2 gene function in spindle formation or microtubule function during cell division. Since this function is essential to cell division throughout metazoans, this gene and any homologs and derivatives thereof represent excellent tools for use in the development of a wide range of therapeutics including anti-proliferative agents. Analysis of the F08B6.2 gene sequence reveals clear orthologs in human (GenBank Accession No. NP_057625) and Drosophila (GenBank Accession No. AAF52761) which have been described as guanine nucleotide binding proteins. A homolog of F08B6.2 has been identified in rat (GenBank Accession No. AAA73553 or NP_631924). There has been no information linking the genes to spindle formation or microtubule function during cell division. Based on the extremely high sequence conservation at the protein level, it can be concluded that these genes, particularly the orthologs, most likely encode proteins with equivalent function in spindle formation or microtubule function during cell division in their respective species.

EXAMPLE 8: Characterization of the *C. elegans* gene CD4.4

dsRNA was designed and used to specifically silence the expression of the *C. elegans* gene by RNAi, thereby testing its functional involvement in the first round of embryonic cell division in this metazoan species. The dsRNA was synthesized *in vitro* from PCR-amplified wild type genomic DNA fragments of the CD4.4 gene. For PCR, the following primer pair was used: "TAATACGACTCACTATAGGAACTTTTCAGGTCCGCTCAA" with "AATTAACCCTCACTAAAGGCCTGAATAGCCAGATCCGAA" as forward and reverse primers, respectively. The dsRNA was purified, and injected into adult hermaphrodite worms. The phenotypic consequences of the RNAi treatment were documented 24 hours later in the F1 progeny of injected worms, using time-lapse differential interference contrast (DIC) microscopy. Embryo recordings started ~20 minutes after ferilization, while the female pronucleus is completing its meiotic divisions, until the 2 cell stage, ~15 to 20 minutes later.

In the F1 embryos of worms injected with dsRNA, the following highly reproducible phenotypes are observed (Fig. 9). There are areas devoid of yolk granules. Small globular

structures are visible in the cytoplasm (Fig. 9A-F, arrows). The structures seem to bind to microtubules and migrate to the minus end. The phenotype is embryonic lethal.

All observed phenotypes indicate a requirement for CD4.4 gene function in spindle formation or microtubule function during cell division. Since this function is essential to cell division throughout metazoans, this gene and any homologs and derivatives thereof represent excellent tools for use in the development of a wide range of therapeutics including anti-proliferative agents. Analysis of the CD4.4 gene sequence reveals clear orthologs in human (two human orthologs: GenBank Accession No. NP_078943 and CAD38936) and Drosophila (GenBank Accession No. NP_AAF52060) which have had no function ascribed to it until now. In particular, there has been no information linking the orthologs to spindle formation or microtubule function during cell division. Based on the extremely high sequence conservation at the protein level, it can be concluded that these genes most likely encode proteins with equivalent function in spindle formation or microtubule function during cell division in humans and Drosophila, respectively.

EXAMPLE 9: Characterization of the *C. elegans* gene ZK546.1

dsRNA was designed and used to specifically silence the expression of the *C. elegans* gene by RNAi, thereby testing its functional involvement in the first round of embryonic cell division in this metazoan species. The dsRNA was synthesized *in vitro* from PCR-amplified wild type genomic DNA fragments of the ZK546.1 gene. For PCR, the following primer pair was used: "TAATACGACTCACTATAGGGCTGATATGGCAGTTTGGGT" with "AATTAACCCTCACTAAAGGGCAACTGAGCAATCCCATTT" as forward and reverse primers, respectively. The dsRNA was purified, and injected into adult hermaphrodite worms. The phenotypic consequences of the RNAi treatment were documented 24 hours later in the F1 progeny of injected worms, using time-lapse differential interference contrast (DIC) microscopy. Embryo recordings started ~20 minutes after ferilization, while the female pronucleus is completing its meiotic divisions, until the 4 cell stage, ~30 minutes later.

In the F1 embryos of worms injected with dsRNA, the following highly reproducible phenotypes are observed (Fig. 11). The centrosomes detach from the male pronucleus (Fig. 11A) and migrate towards the female pronucleus (Fig. 11B-C, arrows). The spindle fails to integrate the male chromosomal material, resulting in the formation of an extra karyomere in the P1 cell. (Fig. 11D-F, arrows). The AB spindle is initially separated from the chromatin, resulting in a segregation defect (Fig. 11 G-H, arrows). The phenotype is embryonic lethal.

All observed phenotypes indicate a requirement for ZK546.1 gene function in spindle formation or microtubule function during cell division. Since this function is essential to cell division throughout metazoans, this gene and any homologs and derivatives thereof represent excellent tools for use in the development of a wide range of therapeutics including anti-proliferative agents. Analysis of the ZK546.1 gene sequence reveals a clear ortholog in human (GenBank Accession No. NP_056972) and homologs in mouse (GenBank Accession No. XP_109474), rat (GenBank Accession No. AAA74950), Drosophila (GenBank Accession No. AAF53605), and Saccharomyces cerevisiae (GenBank Accession No. NP_010225). The murine homolog (Hook1) functions in positioning of microtubular structures within the spermatid. However, there has been no information linking the genes to spindle formation or microtubule function during cell division. Based on the extremely high sequence conservation at the protein level, it can be concluded that these genes, particularly the orthologs, most likely encode proteins with equivalent function in spindle formation or microtubule function during cell division in their respective species.

EXAMPLE 10: Characterization of the *C. elegans* gene C56C10.3

dsRNA was designed and used to specifically silence the expression of the *C. elegans* gene by RNAi, thereby testing its functional involvement in the first round of embryonic cell division in this metazoan species. The dsRNA was synthesized *in vitro* from PCR-amplified wild type genomic DNA fragments of the C56C10.3 gene. For PCR, the following primer pair was used: "TAATACGACTCACTATAGGTTCGGGAAACAGAGGAGATG" with

"AATTAACCCTCACTAAAGGCCTTGTCAGCTTCTTTCGCT" as forward and reverse primers, respectively. The dsRNA was purified, and injected into adult hermaphrodite worms. The phenotypic consequences of the RNAi treatment were documented 24 hours later in the F1 progeny of injected worms, using time-lapse differential interference contrast (DIC) microscopy. Embryo recordings started ~20 minutes after ferilization, while the female pronucleus is completing its meiotic divisions, until the 4 cell stage, ~30 minutes later.

In the F1 embryos of worms injected with dsRNA, the following highly reproducible phenotypes are observed (Fig. 13). There are structures visible in the cytoplasm that seem to bind to astral microtubules or might resemble microtubule bundles. Arrows indicate aberrant structures along astral microtubules.

All observed phenotypes indicate a requirement for C56C10.3 gene function in spindle formation or microtubule function during cell division. Since this function is essential to cell division throughout metazoans, this gene and any homologs and derivatives thereof represent excellent tools for use in the development of a wide range of therapeutics including anti-proliferative agents. Analysis of the C56C10.3 gene sequence reveals clear orthologs in human (GenBank Accession No. XP_059282.3), mouse (GenBank Accession No. NP_083638.1), and Drosophila (GenBank Accession No. NP_610462), and a homolog in yeast (GenBank accession No. NP_013125). The function of these proteins is unknown. In particular, there has been no information linking the genes to spindle formation or microtubule function during cell division. Based on the extremely high sequence conservation at the protein level, it can be concluded that these orthologs most likely encode proteins with equivalent function in spindle formation or microtubule function during cell division in their respective species.

EXAMPLE 11: Effects of RNAi treatment in human cells

Design and synthesis of siRNAs

For all experiments in human cells short double stranded interfering RNAs (siRNAs) of 21 bases in length, comprised of a 19 bp core of complementary sequence and 2 bases

overhang at the 3' end, were designed by Cenix and chemically synthesized by Ambion Inc., Austin, Texas, USA.

The following siRNA sequences were used:

scrambled negative control	5-AGUACUGCUUACGAUACGGTT-3 3-TTUCAUGACGAAUGCUAUGCC-5
positive control (PCNA, proliferating cell nuclear antigen)	5-GGAGAAAGUUUCAGACUAUTT-3 3-GTCCUCUUUCAAAGUCUGAUA-5
NP_056972.1	5-GGUUGCUCCAGCUUAUUUUTT-3 3-CTCCAACGAGGUCGAAUAAAA-5
CAD38936	5-GGUUCUCUUUGAAGCCUAUTT-3 3-GTCCAAGAGAAACUUCGGAUA-5
NP_060387.1	5-GGCUUCAGGGAAAAUACUGTT-3 3-TTCCGAAGUCCCUUUUAUGAC-5
NP_076974.1	5-GGACCCUAGUAGAGAUGAATT-3 3-CTCCUGGGAUCAUCUCUACUU-5
NP_060658.1	5-GUCCCACAGGUGCCUCAUUTT-3 3-TTCAGGGUGUCCACGGAGUAA-5

Transfection

HeLa cells were treated with siRNAs at a final concentration of 100nM using a lipofection based transfection protocol.

24 h before transfection, HeLa cells were seeded in 96well plates at a density of 6,000 cells/well.

On the day of transfection, the transfection mix was prepared as follows: 1 µl of a 10 µM stock of siRNA was diluted with 16 µl of Opti-MEM (Invitrogen Inc.), and 0.4 µl Oligofectamine transfection reagent (Invitrogen) were diluted with 2.4 µl of Opti-MEM.

For complex formation, both solutions were gently mixed and incubated for 20 min at RT. Culture medium was removed from the cells and 80 µl of fresh medium (DMEM, Invitrogen) were added, followed by addition of 20 µl of transfection mix. Cells were incubated at 37°C for 4 hours, 50 µl of fresh medium, supplemented with 30 % fetal calf serum were added, followed by another incubation for 48-72 hours.

Determination of silencing level by quantitative RT-PCR (qRT-PCR)

48 hours after transfection, total RNA was extracted from RNAi treated cells using Invisorb kits (Invitek GmbH, Berlin), and cDNA was produced with ABI TaqMan reverse transcription reagents (Applied Biosystems, USA). In both cases the manufacturer's instructions were followed. Quantitative real-time PCR was performed using the following protocol: 5.5µl of 2x SybrGreen PCR mix (Applied Biosystems) were mixed with 3 µl of sample cDNA and 2.5 µl of a 2 µM solution of gene specific PCR primers, followed by incubation in a ABI-7900-HT real-time PCR machine at 50°C 2min - 95°C 10min - 45 cycles (95°C 15sec - 60°C 1min) - 95°C 15sec - 60°C 15sec - 95°C 15sec. In addition to the gene specific reaction, a second, reference reaction was run for each cDNA sample, using primers for 18S rRNA. Amplification signals from different gene specific samples were normalized using the reference values on 18S rRNA for these respective samples, and compared to samples from control (scrambled siRNA from Ambion Inc.) treated cells.

Proliferation assay

In order to quantify the number of living cells after RNAi treatment, ATP levels were measured 72h after transfection using the ATPlite assay (Perkin Elmer). Cells were extracted and treated according to the manufacturer's instructions. Luminescence read out was performed on a Victor 2 multi label reader (Perkin Elmer). For graphical presentation purposes the proliferation of untreated cells was set to 100.

Apoptosis assay

The levels of programmed cell death in RNAi treated cells were determined 72 hours after transfection, using the Caspase 3/7 specific fluorometric assay ApoOne by Promega, following the manufacturer's instructions. Read out was performed on a Victor 2 multi label reader (Perkin Elmer). For graphical presentation purposes the apoptosis rate of untreated cells was set to 100.

Mitotic Index (MI)

Phosphorylation at serin 10 of histone H3 is considered a hallmark of mitosis, appearing in early prophase and disappearing during telophase. Using immunofluorescence microscopy, mitotic cells can be revealed by an increased binding of a phospho-histone H3 antibody, detected by a suitable fluorescence labelled secondary antibody.

RNAi treated cells in 96 well microscopy plates were stained using the following protocol: Cells were washed with PBS and fixed with 4% para-formaldehyde for 30 min at RT, followed by three washes with PBS. Cells were then permeabilised and blocked in the presence of 0.1% Triton X-100 and 2% BSA for 30 min. The supernatant was removed and anti Phospho Histone H3 (mouse monoclonal antibody clone 6G3, Cell Signalling Technologies) was added at a dilution of 1:750 for 2 hours at RT, followed by three washes with PBS. For detection of Phosph Histone H3 labelled nuclei, goat anti mouse antibody (1:500), coupled to Alexa Fluor 568 (Molecular Probes) was added in a solution supplemented with 0.5 µg/ml Dapi (4',6-diamidino-2-phenylindole, dihydrochloride), FluoroPure™ grade, Molecular Probes) for detection of all nuclei. After incubation for 2 hours at RT, cells were washed four times and images were taken using an automated microscopy system (Discovery-1, Universal Imaging Inc.), acquiring a minimum of 6 images/well. Metamorph-HCS image processing software was used to determine the numbers of mitotic and overall nuclei. The Mitotic Index resembles the fraction of mitotic over all nuclei in a given cell population. For graphical presentation purposes the MI of untreated cells was set to 100.

Effects of RNAi treatment

As shown in Fig. 17, RNAi treatment of HeLa cells using an siRNA directed against NP_056972.1, the human ortholog of C. elegans gene ZK546.1, results in a 50% reduction of cell proliferation and a subtle decrease of Mitotic Index compared to control treated cells. RNAi treatment of HeLa cells using an siRNA directed against CAD38936, the human ortholog of C. elegans gene CD4.4, results in a 60% reduction of cell proliferation, a significant induction of apotosis and a 2.5fold decrease in the Mitotic Index compared to control treated cells. RNAi treatment of HeLa cells using an siRNA directed against NP_076974.1, the human ortholog of C. elegans gene C13F10.2, results in a 40% reduction in cell proliferation, a 2fold increase in the rate of apoptosis and a significant

increase in the Mitotic Index compared to control treated cells. RNAi treatment of HeLa cells using an siRNA directed against NP_060658.1, the human ortholog of C. elegans gene F54B3.3, results in a 70% reduction of cell proliferation, a 2.5fold increase in the rate of apoptosis compared to control treated cells.

5

Claims

1. The use of an isolated nucleic acid molecule comprising a nucleic acid molecule with a sequence selected from the group of sequences consisting of:

a) the nucleic acid sequences presented in SEQ ID NO. 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59;

b) nucleic acid sequences encoding polypeptides that exhibit a sequence identity with the protein encoded by a nucleic acid according to a) of at least 25 % over 100 residues and/or which are detectable in a computer aided search using the BLAST sequence analysis programs with an e-value of at most 10^{-5},

c) sequences of nucleic acid molecules which are capable of hybridizing with the nucleic acid molecules with sequences corresponding to (a) or (b) under conditions of medium or high stringency,

d) the antisense-sequence of any of the sequences as defined in (a), (b) or (c),

e) fragments of (a), (b), (c) or (d),

f) double-stranded RNA or single-stranded RNA in the antisense or sense direction corresponding to any of the sequences as defined in (a), (b), (c), (d), or (e).

for the manufacture of a medicament for the inhibition of spindle formation or microtubule function during cell division.

2. The use according to claim 1, wherein the isolated nucleic acid molecule comprises small interfering RNA with a sequence corresponding to any of the sequences according to claim 1.

3. The use according to claim 1, wherein the nucleic acid molecule is contained in at least one nucleic acid expression vector which is capable of producing a double-stranded RNA-molecule comprising a sense-RNA-strand and an antisense-RNA-strand under suitable conditions, wherein each RNA-strand, independently from the other, has a length of 19 to 31 nucleotides.

4. The use according to claim 1, wherein the nucleic acid molecule is contained in at least one nucleic acid expression vector comprising a first expression cassette containing the nucleic acid corresponding to the sense-RNA-strand under the control of a first promoter and a second expression cassette containing the nucleic acid corresponding to the antisense-RNA-strand under the control of a second promoter.

5. The use according to claim 1, wherein the nucleic acid molecule is contained in at least one nucleic acid expression vector comprising an expression cassette containing the nucleic acid corresponding to the sense-RNA-strand and the antisense-RNA-strand under the control of a promoter leading to a single-stranded RNA-molecule and wherein the single-stranded RNA-molecule is capable of forming a back-folded stem-loop-structure.

6. The use according to any of claims 2 to 5, wherein each RNA-strand, independently from the other, has a length of 20 to 25, preferably of 20 to 22 nucleotides.

7. The use according to any of claims 2 to 5, wherein each RNA-strand, independently from the other, has a length of 26 to 28, preferably of 27 nucleotides.

8. The use of a an isolated peptide or polypeptide comprising a peptide or polypeptide with a sequence selected from the group consisting of:

(a) a sequence as disclosed in SEQ ID NO. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60;
(b) a sequence that exhibits a sequence identity with any of the sequences according to (a) of at least 25 % over 100 residues,
(c) fragments of the sequences defined in (a) or (b),

for the manufacture of a medicament for the inhibition of spindle formation or microtubule function during cell division.

9. The use of an antibody which is directed against at least one peptide or polypeptide with a sequence as defined in claim 8 for the manufacture of a medicament for the inhibition of spindle formation or microtubule function during cell division.

10. The use according to any of claims 1 to 9, wherein the medicament is for the therapy of a proliferative disease.

11. The use according to claim 10, wherein the disease is coronary restenosis or a neoplastic disease, the latter preferably selected from the group consisting of lymphoma, lung cancer, colon cancer, ovarian cancer and breast cancer.

12. The use of an isolated nucleic acid molecule comprising a nucleic acid with a sequence selected from the group of sequences consisting of:

a) the nucleic acid sequences presented in SEQ ID NO. 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59;
b) nucleic acid sequences encoding polypeptides that exhibit a sequence identity with the protein encoded by a nucleic acid according to a) of at least 25 % over 100 residues and/or which are detectable in a computer aided search using the BLAST sequence analysis programs with an e-value of at most 10^{-5},
c) sequences of nucleic acid molecules which are capable of hybridizing with the nucleic acid molecules with sequences corresponding to (a) or (b) under conditions of medium or high stringency,
d) the antisense-sequence of any of the sequences as defined in (a), (b) or (c),
e) fragments of (a), (b), (c) or (d),
f) RNA sequences corresponding to any of the sequences as defined in (a), (b), (c), (d), or (e),

for the manufacture of a medicament for the activation of spindle formation or microtubule function during cell division.

13. The use of a an isolated peptide or polypeptide comprising a peptide or polypeptide with a sequence selected from the group consisting of:

(a) a sequence as disclosed in SEQ ID NO. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60;

(b) a sequence that exhibits a sequence identity with any of the sequences according to (a) of at least 25 % over 100 residues,

(c) fragments of the sequences defined in (a) or (b),

for the manufacture of a medicament for the activation of spindle formation or microtubule function during cell division.

14. The use of an antibody which is directed against at least one peptide or polypeptide with a sequence as defined in claim 8 for the manufacture of a medicament for the activation of spindle formation or microtubule function during cell division.

15. The use according to any of claims 12 to 14, wherein the medicament is for the treatment of a disease characterized by increased apoptosis, growth retardation, or slowed wound healing.

16. A medicament containing an isolated nucleic acid molecule, peptide, polypeptide, or antibody selected from the group consisting of

a) nucleic acid molecules or nucleic acid expression vectors as defined in any of claims 1 to 7,

b) a peptide or polypeptide comprising a sequence as defined in claim 8,

c) an antibody directed against at least one peptide or polypeptide according to (b).

17. The use of an isolated nucleic acid molecule comprising a sequence as defined in claim 1 or the use of a ligand binding specifically at least one polypeptide comprising a sequence as defined in claim 8 for the in vitro diagnosis of a proliferative disease or a disease associated with abnormal spindle formation or microtubule function during cell division.

18. The use according to claim 17, wherein the disease is coronary restenosis or a neoplastic disease, the latter preferably selected from the group consisting of lymphoma, lung cancer, colon cancer, ovarian cancer and breast cancer.

19. A diagnostic kit containing an isolated nucleic acid molecule as defined in claim 1 or 2 and/or a ligand which is directed against at least one polypeptide as defined in claim 8 for the in vitro diagnosis of a proliferative disease or a disease associated with abnormal spindle formation or microtubule function during cell division.

20. The use of an isolated nucleic acid molecule or a nucleic acid expression vectors as defined in any of claims 1 to 7 or of an antibody which is directed against at least one polypeptide comprising a sequence as defined in claim 8, in a screening assay for the identification and characterization of drugs that inhibit or activate spindle formation or microtubule function during cell division.

21. The use of a polypeptide with a sequence as defined in claim 8 in a screening assay for interacting drugs that inhibit or activate spindle formation or microtubule function during cell division.

22. A screening method for the identification and characterization of an inhibitor or an activator molecule that inhibits or activates spindle formation or microtubule function during cell division comprising the following steps:

a) transformation of a nucleic acid molecule or a nucleic acid expression vector as defined in any of claims 1 to 7 into a host cell or host organism,

b) cultivation of the host cell or host organism obtained in step a) under conditions that allow the overexpression of the polypeptide or RNA encoded by or corresponding to the nucleic acid of step a) either in the presence or in the absence of at least one candidate for an inhibitor- or activator-molecule, and

c) analysis of the spindle formation or microtubule function during cell division in the cultivated cell or organism and thereby identification of an inhibitor or activator of spindle formation or microtubule function during cell division.

23. A screening method for the identification and characterization of an interacting molecule that inhibits or activates spindle formation or microtubule function during cell division from a library of test substances comprising the following steps:

a) recombinantly expressing a polypeptide encoded by a nucleic acid molecule sequence as defined in claim 1 in a host cell,

b) isolating and optionally purifying the recombinantly expressed polypeptide of step (a),

c) optionally labelling of the test substances and/or labelling of the recombinantly expressed polypeptide,

d) immobilizing the recombinantly expressed polypeptide to a solid phase,

e) contacting of at least one test substance with the immobilized polypeptide,

f) optionally one or more washing steps,

g) detecting the binding of the at least one test substance to the immobilized polypeptid at the solid phase, and

g) performing a functional assay for inhibition or activation of spindle formation or microtubule function during cell division.

24. A method for the preparation of a pharmaceutical composition wherein an inhibitor or activator of spindle formation or microtubule function during cell division is identified according to claim 22 or 23, synthesized in adequate amounts, and formulated into a pharmaceutical composition.

25. A method for the preparation of a pharmaceutical composition wherein an inhibitor or activator of spindle formation or microtubule function during cell division is provided according to claim 22 or 23 and formulated into a pharmaceutical composition.

C13F10.2

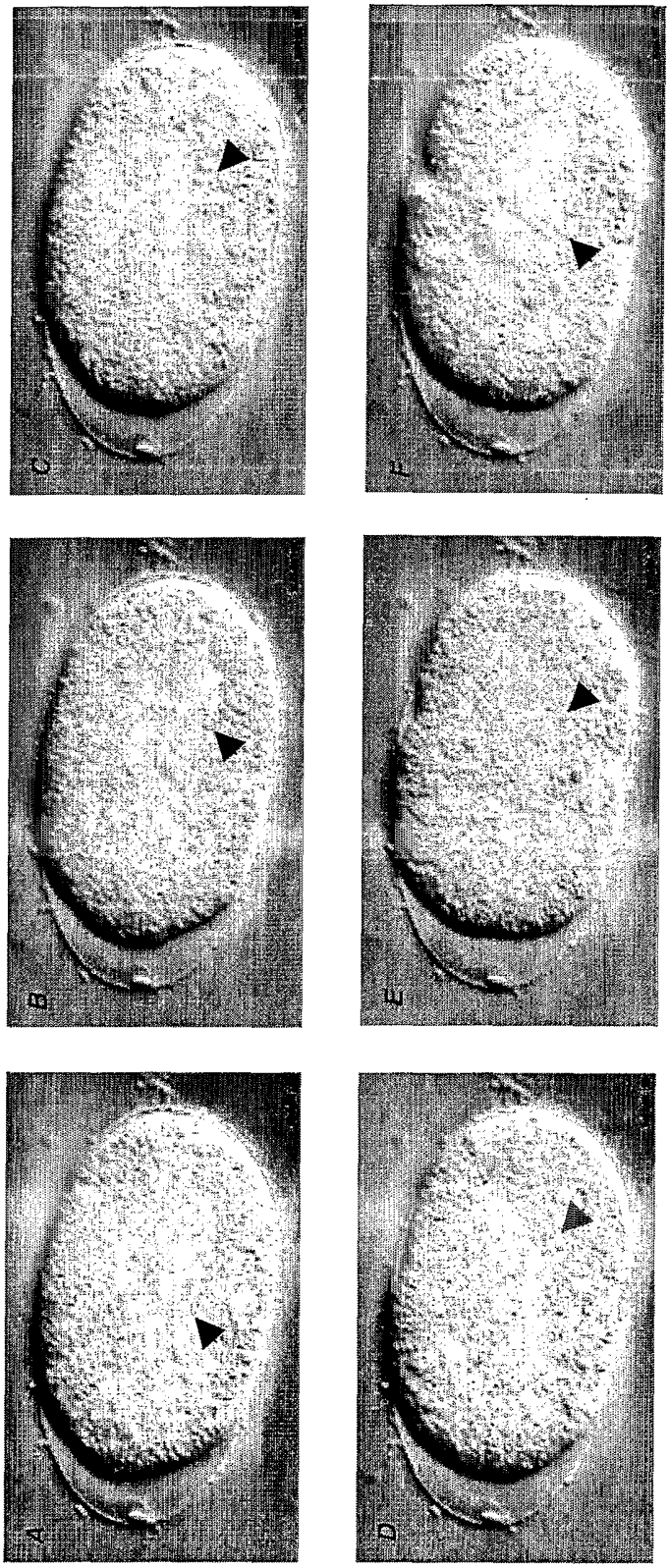

Fig.1

Fig. 2

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CLUSTAL W (1.8) multiple sequence alignment


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C13F10.2        MAEKNHQQQERLPGNPFFPSRSNAGSSFDMPETPHLIDSLTSQIDEFTIQSIIDTQRQSL
                                     .:  . :  :   : . ::   ::::* :*:: *.

NP_076974       DRFEKTNEMLLNFNNLSSARLQQMSERFLHHTRTLVEMKRDLDSIFRRIRTLKGKLARQH
AAF49911        QRFEKTNEMLLNCNALSQSRLKSASEDFKRHVKCLSEMKKDLDYIFRKIRIIKQKLQSQF
C13F10.2        KRFEKTNEMLMNCAQLGDRRIEKAKRDSVGHKETILQMKTDLEFIFKKIRMFKTVLSSKY
                **********:*   *.. *::. ..    * . : :** **: **::** :*  *  :.*

NP_076974       PEAFSHI-PEASFLEEEDEDPIPPSTTTTIATSEQSTG----SCDTSPDTVSPSLSPGFE
AAF49911        PAIYAEVQPQRSSLAEEAEDDTEAQAKKTAETPAPAAAKPVLSTKKSAATIEYVQMEEAV
C13F10.2        PEVYAEVSAELTPKRSEEDE----------------------------------------
                  ::.: .: :   .* ::

NP_076974       DLSHVQAGSPAIN------GRSQTDDEEMTGE---
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C13F10.2        ------------------------------------
                                        *
```

Fig.3

C25A1.9

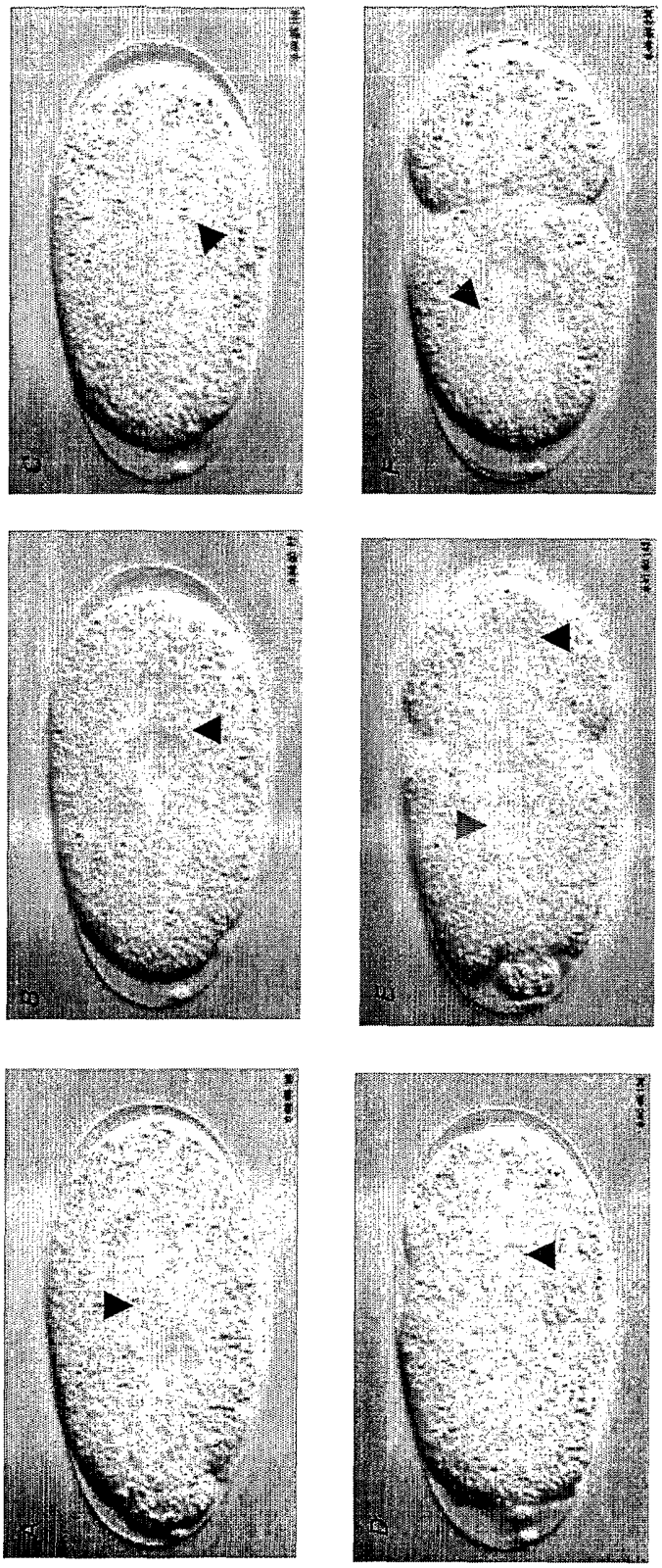

Fig. 4

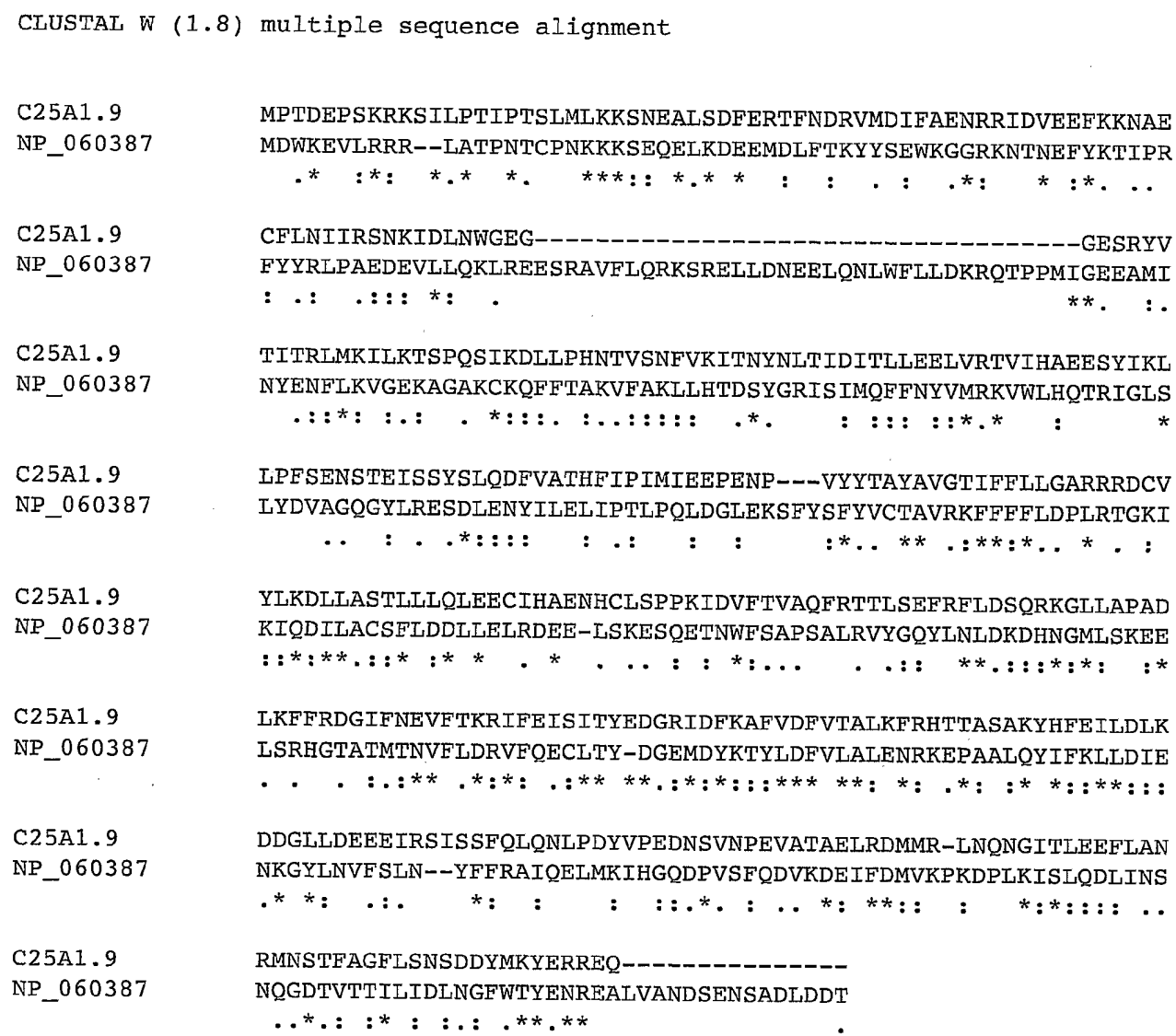
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Fig. 5

F54B3.3

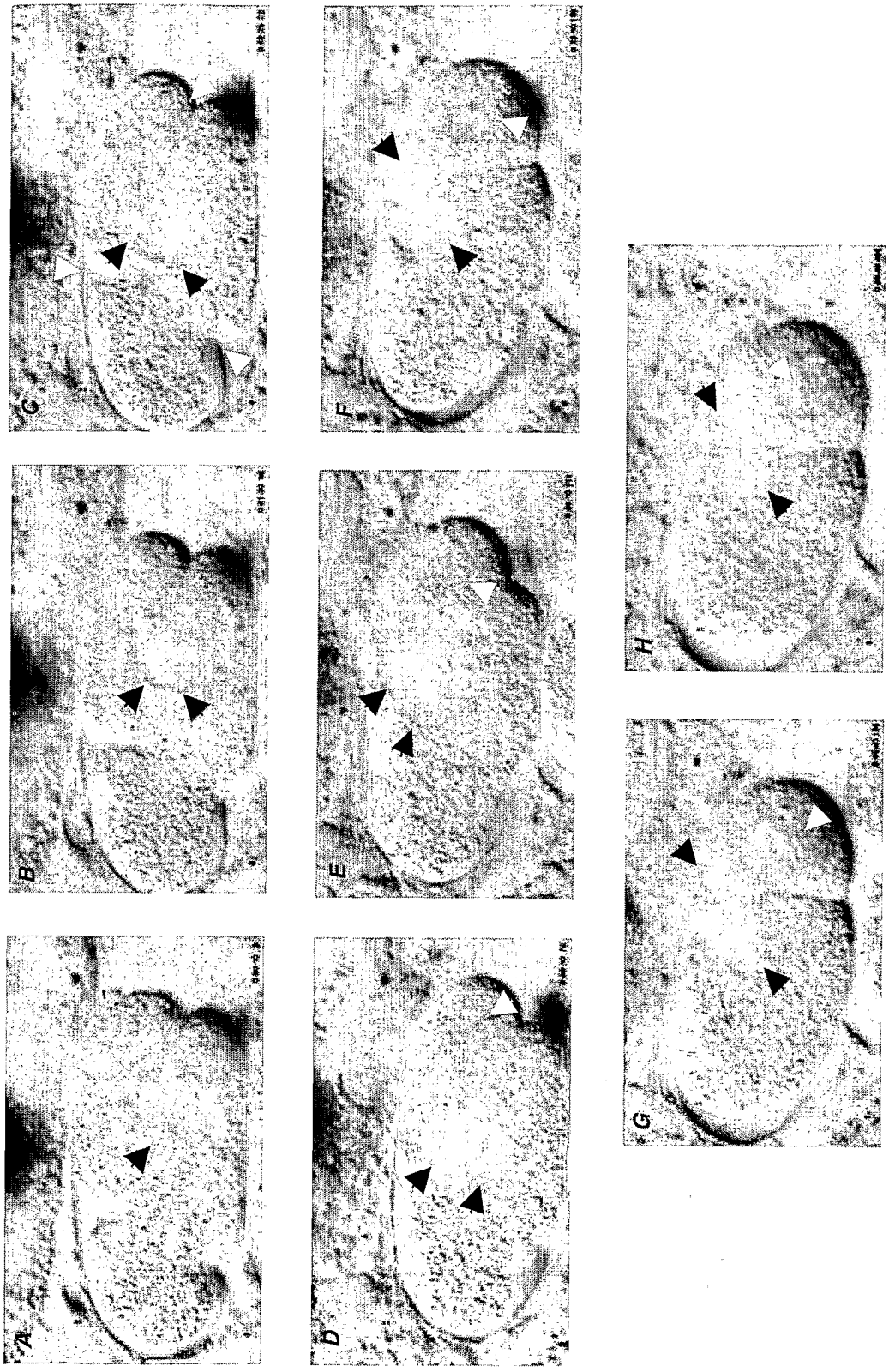
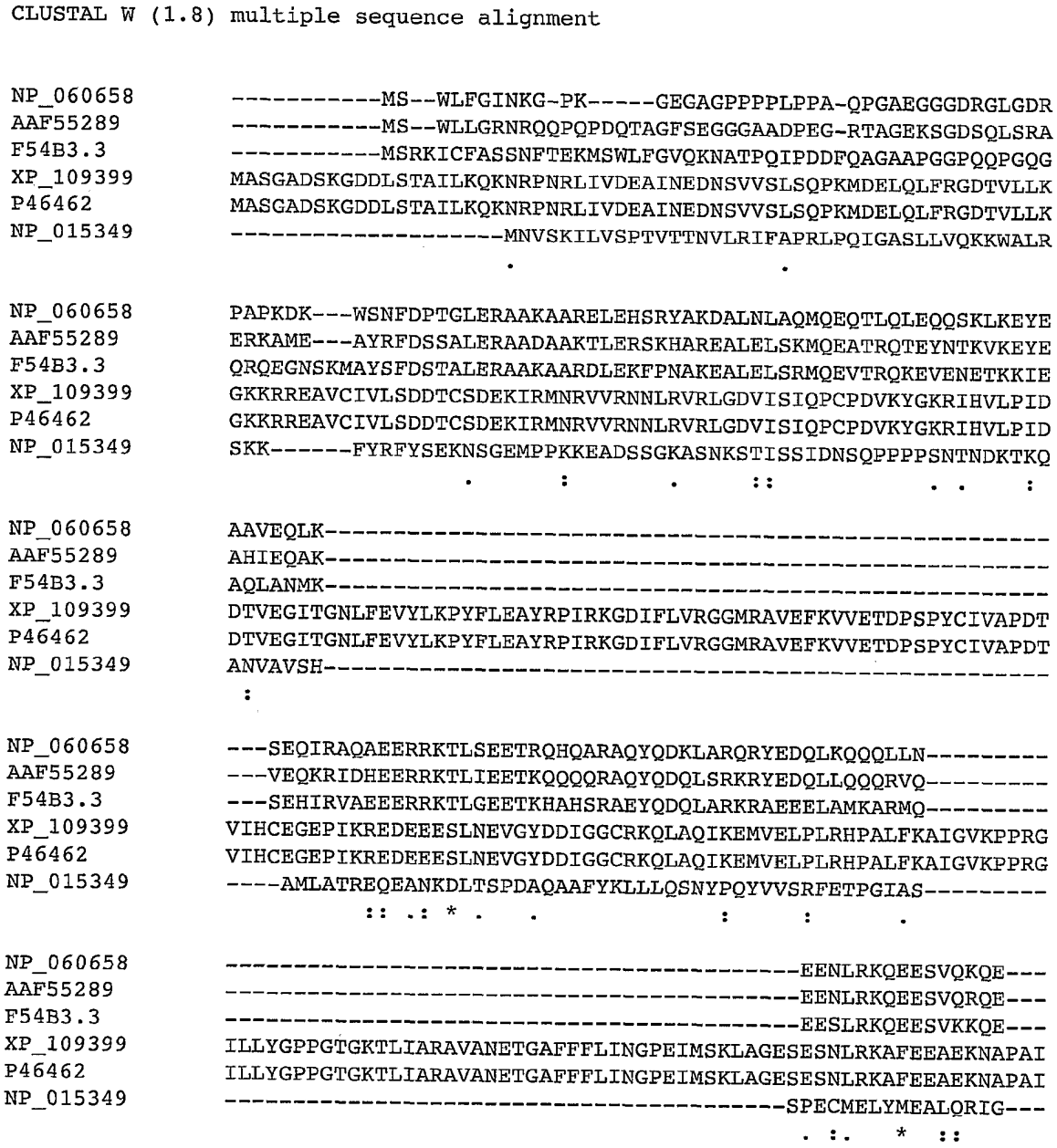


Fig. 6 1/3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AAF55289 ----------MS--WLLGRNRQQPQPDQTAGFSEGGGAADPEG-RTAGEKSGDSQLSRA
F54B3.3 ----------MSRKICFASSNFTEKMSWLFGVQKNATPQIPDDFQAGAAPGGPQQPGQG
XP_109399 MASGADSKGDDLSTAILKQKNRPNRLIVDEAINEDNSVVSLSQPKMDELQLFRGDTVLLK
P46462 MASGADSKGDDLSTAILKQKNRPNRLIVDEAINEDNSVVSLSQPKMDELQLFRGDTVLLK
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P46462 GKKRREAVCIVLSDDTCSDEKIRMNRVVRNNLRVRLGDVISIQPCPDVKYGKRIHVLPID
NP_015349 SKK------FYRFYSEKNSGEMPPKKEADSSGKASNKSTISSIDNSQPPPPSNTNDKTKQ
NP_060658 AAVEQLK----------
AAF55289 AHIEQAK----------
F54B3.3 AQLANMK----------
XP_109399 DTVEGITGNLFEVYLKPYFLEAYRPIRKGDIFLVRGGMRAVEFKVVETDPSPYCIVAPDT
P46462 DTVEGITGNLFEVYLKPYFLEAYRPIRKGDIFLVRGGMRAVEFKVVETDPSPYCIVAPDT
NP_015349 ANVAVSH----------
NP_060658 ---SEQIRAQAEERRKTLSEETRQHQARAQYQDKLARQRYEDQLKQQQLLN---------
AAF55289 ---VEQKRIDHEERRKTLIEETKQQQQRAQYQDQLSRKRYEDQLLQQQRVQ---------
F54B3.3 ---SEHIRVAEEERRKTLGEETKHAHSRAEYQDQLARKRAEEELAMKARMQ---------
XP_109399 VIHCEGEPIKREDEEESLNEVGYDDIGGCRKQLAQIKEMVELPLRHPALFKAIGVKPPRG
P46462 VIHCEGEPIKREDEEESLNEVGYDDIGGCRKQLAQIKEMVELPLRHPALFKAIGVKPPRG
NP_015349 ----AMLATREQEANKDLTSPDAQAAFYKLLLQSNYPQYVVSRFETPGIAS---------
NP_060658 ----------EENLRKQEESVQKQE---
AAF55289 ----------EENLRKQEESVQRQE---
F54B3.3 ----------EESLRKQEESVKKQE---
XP_109399 ILLYGPPGTGKTLIARAVANETGAFFFLINGPEIMSKLAGESESNLRKAFEEAEKNAPAI
P46462 ILLYGPPGTGKTLIARAVANETGAFFFLINGPEIMSKLAGESESNLRKAFEEAEKNAPAI
NP_015349 ----------SPECMELYMEALQRIG---

Fig. 6 2/3

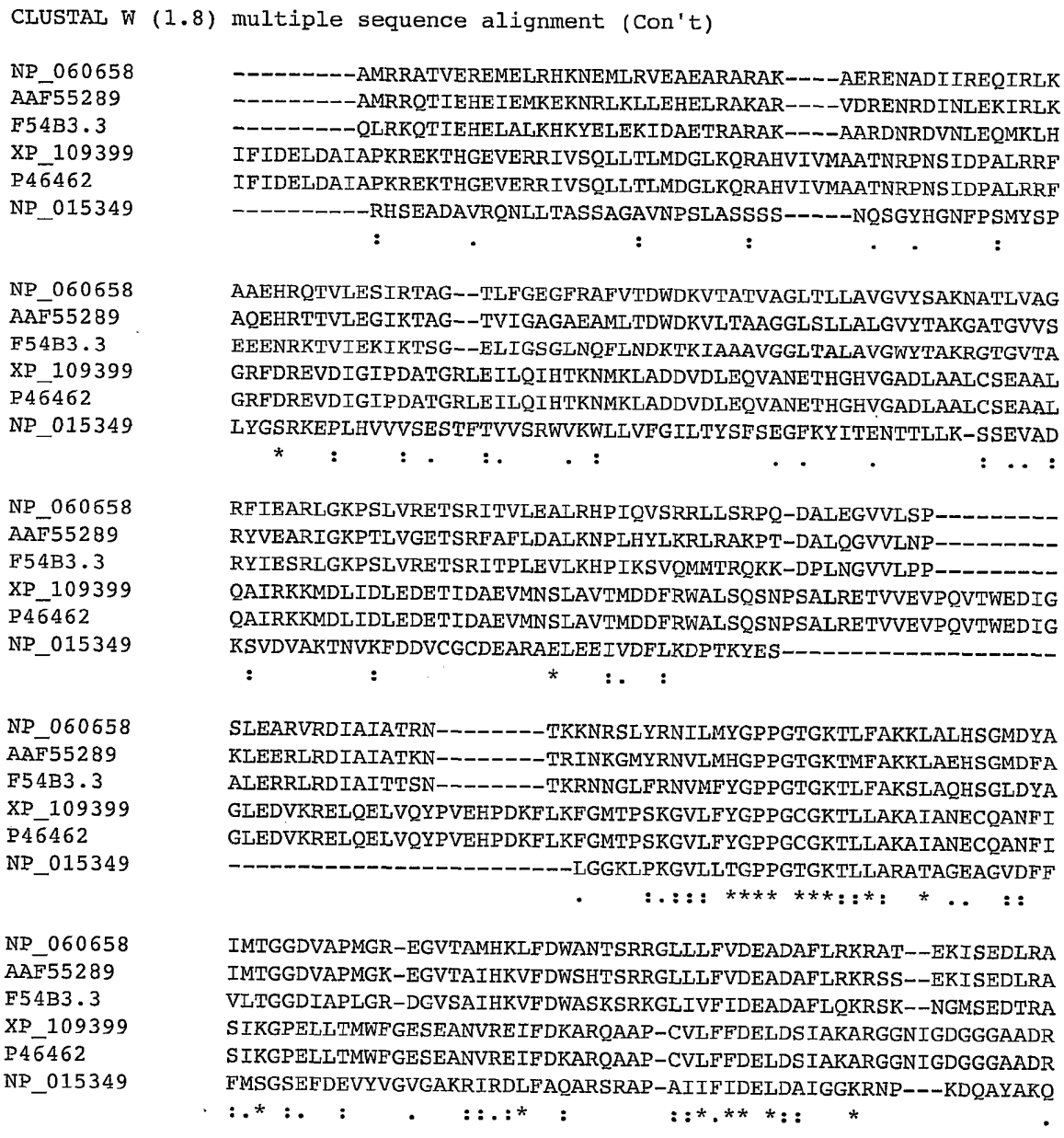
CLUSTAL W (1.8) multiple sequence alignment (Con't)
NP_060658 ---------AMRRATVEREMELRHKNEMLRVEAEARARAK----AERENADIIREQIRLK
AAF55289 ---------AMRRQTIEHEIEMKEKNRLKLLEHELRAKAR----VDRENRDINLEKIRLK
F54B3.3 ---------QLRKQTIEHELALKHKYELEKIDAETRARAK----AARDNRDVNLEQMKLH
XP_109399 IFIDELDAIAPKREKTHGEVERRIVSQLLTLMDGLKQRAHVIVMAATNRPNSIDPALRRF
P46462 IFIDELDAIAPKREKTHGEVERRIVSQLLTLMDGLKQRAHVIVMAATNRPNSIDPALRRF
NP_015349 ----------RHSEADAVRQNLLTASSAGAVNPSLASSSS-----NQSGYHGNFPSMYSP
NP_060658 AAEHRQTVLESIRTAG--TLFGEGFRAFVTDWDKVTATVAGLTLLAVGVYSAKNATLVAG
AAF55289 AQEHRTTVLEGIKTAG--TVIGAGAEAMLTDWDKVLTAAGGLSLLALGVYTAKGATGVVS
F54B3.3 EEENRKTVIEKIKTSG--ELIGSGLNQFLNDKTKIAAAVGGLTALAVGWYTAKRGTGVTA
XP_109399 GRFDREVDIGIPDATGRLEILQIHTKNMKLADDVDLEQVANETHGHVGADLAALCSEAAL
P46462 GRFDREVDIGIPDATGRLEILQIHTKNMKLADDVDLEQVANETHGHVGADLAALCSEAAL
NP_015349 LYGSRKEPLHVVVSESTFTVVSRWVKWLLVFGILTYSFSEGFKYITENTTLLK-SSEVAD
NP_060658 RFIEARLGKPSLVRETSRITVLEALRHPIQVSRRLLSRPQ-DALEGVVLSP---------
AAF55289 RYVEARIGKPTLVGETSRFAFLDALKNPLHYLKRLRAKPT-DALQGVVLNP---------
F54B3.3 RYIESRLGKPSLVRETSRITPLEVLKHPIKSVQMMTRQKK-DPLNGVVLPP---------
XP_109399 QAIRKKMDLIDLEDETIDAEVMNSLAVTMDDFRWALSQSNPSALRETVVEVPQVTWEDIG
P46462 QAIRKKMDLIDLEDETIDAEVMNSLAVTMDDFRWALSQSNPSALRETVVEVPQVTWEDIG
NP_015349 KSVDVAKTNVKFDDVCGCDEARAELEEIVDFLKDPTKYES----------
NP_060658 SLEARVRDIAIATRN--------TKKNRSLYRNILMYGPPGTGKTLFAKKLALHSGMDYA
AAF55289 KLEERLRDIAIATKN--------TRINKGMYRNVLMHGPPGTGKTMFAKKLAEHSGMDFA
F54B3.3 ALERRLRDIAITTSN--------TKRNNGLFRNVMFYGPPGTGKTLFAKSLAQHSGLDYA
XP_109399 GLEDVKRELQELVQYPVEHPDKFLKFGMTPSKGVLFYGPPGCGKTLLAKAIANECQANFI
P46462 GLEDVKRELQELVQYPVEHPDKFLKFGMTPSKGVLFYGPPGCGKTLLAKAIANECQANFI
NP_015349 ----------LGGKLPKGVLLTGPPGTGKTLLARATAGEAGVDFF
NP_060658 IMTGGDVAPMGR-EGVTAMHKLFDWANTSRRGLLLFVDEADAFLRKRAT--EKISEDLRA
AAF55289 IMTGGDVAPMGK-EGVTAIHKVFDWSHTSRRGLLLFVDEADAFLRKRSS--EKISEDLRA
F54B3.3 VLTGGDIAPLGR-DGVSAIHKVFDWASKSRKGLIVFIDEADAFLQKRSK--NGMSEDTRA
XP_109399 SIKGPELLTMWFGESEANVREIFDKARQAAP-CVLFFDELDSIAKARGGNIGDGGGAADR
P46462 SIKGPELLTMWFGESEANVREIFDKARQAAP-CVLFFDELDSIAKARGGNIGDGGGAADR
NP_015349 FMSGSEFDEVYVGVGAKRIRDLFAQARSRAP-AIIFIDELDAIGGKRNP---KDQAYAKQ

Fig. 6 3/3

```
CLUSTAL W (1.8) multiple sequence alignment (Con't)

NP_060658       TLNAFLYRTG--QHSNKFMLVLASNQPEQFDWAIN--DRINEMVHFDLPGQEERERLVRM
AAF55289        ALNAFLYRTS--EQNPKFMLVLASNTPEQFDYAIN--DRLDEMVEFTLPGLEERERLLRL
F54B3.3         ALNAFLFRTG--EQSRKFMLVVASNQPEQFDWAVN--DRFDQLVEFTLPGMEERERILLQ
XP_109399       VINQILTEMDGMSTKKNVFIIGATNRPDIIDPAILRPGRLDQLIYIPLPDEKSRVAILKA
P46462          VINQILTEMDGMSTKKNVFIIGATNRPDIIDPAILRPGRLDQLIYIPLPDEKSRVAILKA
NP_015349       TLNQLLVELDGFSQTSGIIIIGATNFPEALDKALTRPGRFDKVVNVDLPDVRGRADILKH
                :* :* . .  . .  .::: *:* *: :* *:   .*:::::. . **. . *  ::

NP_060658       YFDKYVLKPATEGK--QRLK--LAQFDYGRKCSEVARLTEGMSGREIAQLAVSWQA--TA
AAF55289        YFDKYVLQPAAAGA--KRFK--LDTFDYGKTCSKMAALCEGMSGREISKLGVSWQA--AV
F54B3.3         YFNEHIVTPATSGSRSQRLK--LDNFDWVAKCNEVAKKTSGMSGRELSKLVIGWQA--SA
XP_109399       NLRKSPVAKDVDLEFLAKMTNGFSGADLTEICQRACKLAIRESIESEIRRERERQTNPSA
P46462          NLRKSPVAKDVDLEFLAKMTNGFSGADLTEICQRACKLAIRESIESEIRRERERQTNPSA
NP_015349       HMKKITLADNVDPTIIARGTPGLSGAELANLVNQAAVYACQKNAVSVDMSHFEWAKDKIL
                : :  :   .     : .  :   :     .. .     .  .

NP_060658       YASEDG---------------VLTEAMMDTRVQDAVQQHQQK-----------------
AAF55289        YASEDG---------------LLTEKMVLDRCYSAAQQHKQKRWPG------------FR
F54B3.3         YASETG---------------VLTEAIVDRNTADAMVQHEHK-MEW------------LE
XP_109399       MEVEED---------------DPVPEIRRDHFEEAMRFARRSVSDND-----------IR
P46462          MEVEED---------------DPVPEIRRDHFEEAMRFARRSVSDND-----------IR
NP_015349       MGAERKTMVLTDAARKATAFHEAGHAIMAKYTNGATPLYKATILPRGRALGITFQLPEMD
                  *                       :      *    . .

NP_060658       MCWLKAEGP-------------------------GRGDEPSPS----------------
AAF55289        IRSVLITNP-------------------------SQAQLPHPSP---------------
F54B3.3         KEQLKARNQEV---------------------KFGTTLKRETAV---------------
XP_109399       KYEMFAQTLQQ----------------------SRGFGSFRFPSGNQGGAGPSQGSGGGTG
P46462          KYEMFAQTLQQ----------------------SRGFGSFRFPSGNQGGAGPSQGSGGGTG
NP_015349       KVDITKRECQARLDVCMGGKIAEELIYGKDNTTSGCGSDLQSATGTARAMVTQYGMSDDV
                  :                                .      .:
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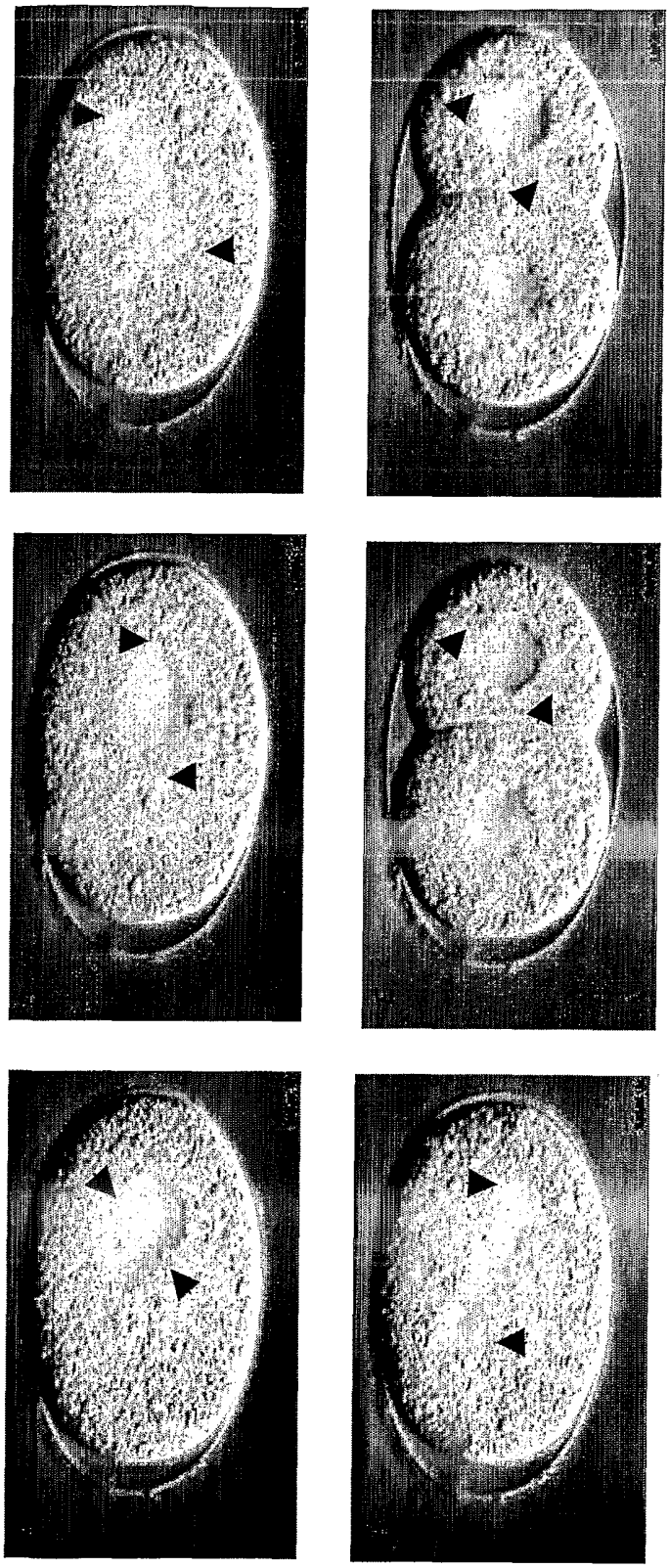

Fig. 7

Fig. 8

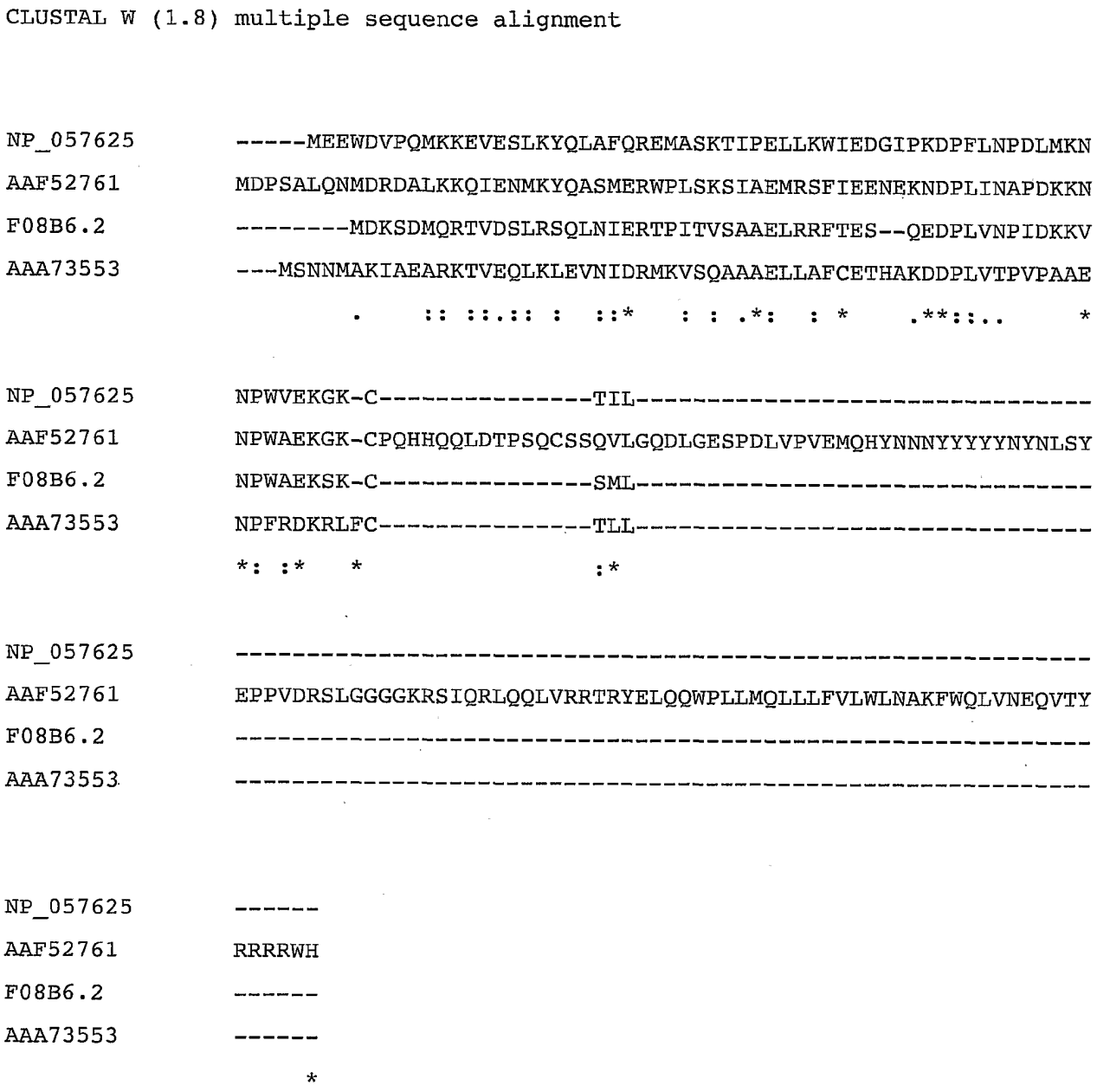
CLUSTAL W (1.8) multiple sequence alignment
NP_057625 -----MEEWDVPQMKKEVESLKYQLAFQREMASKTIPELLKWIEDGIPKDPFLNPDLMKN
AAF52761 MDPSALQNMDRDALKKQIENMKYQASMERWPLSKSIAEMRSFIEENEKNDPLINAPDKKN
F08B6.2 --------MDKSDMQRTVDSLRSQLNIERTPITVSAAELRRFTES--QEDPLVNPIDKKV
AAA73553 ---MSNNMAKIAEARKTVEQLKLEVNIDRMKVSQAAAELLAFCETHAKDDPLVTPVPAAE
NP_057625 NPWVEKGK-C---------------TIL---------------------------------
AAF52761 NPWAEKGK-CPQHHQQLDTPSQCSSQVLGQDLGESPDLVPVEMQHYNNNYYYYYNYNLSY
F08B6.2 NPWAEKSK-C---------------SML---------------------------------
AAA73553 NPFRDKRLFC--------------TLL---------------------------------
NP_057625 --
AAF52761 EPPVDRSLGGGGKRSIQRLQQLVRRTRYELQQWPLLMQLLLFVLWLNAKFWQLVNEQVTY
F08B6.2 --
AAA73553 --
NP_057625 ------
AAF52761 RRRRWH
F08B6.2 ------
AAA73553 ------

Fig. 9

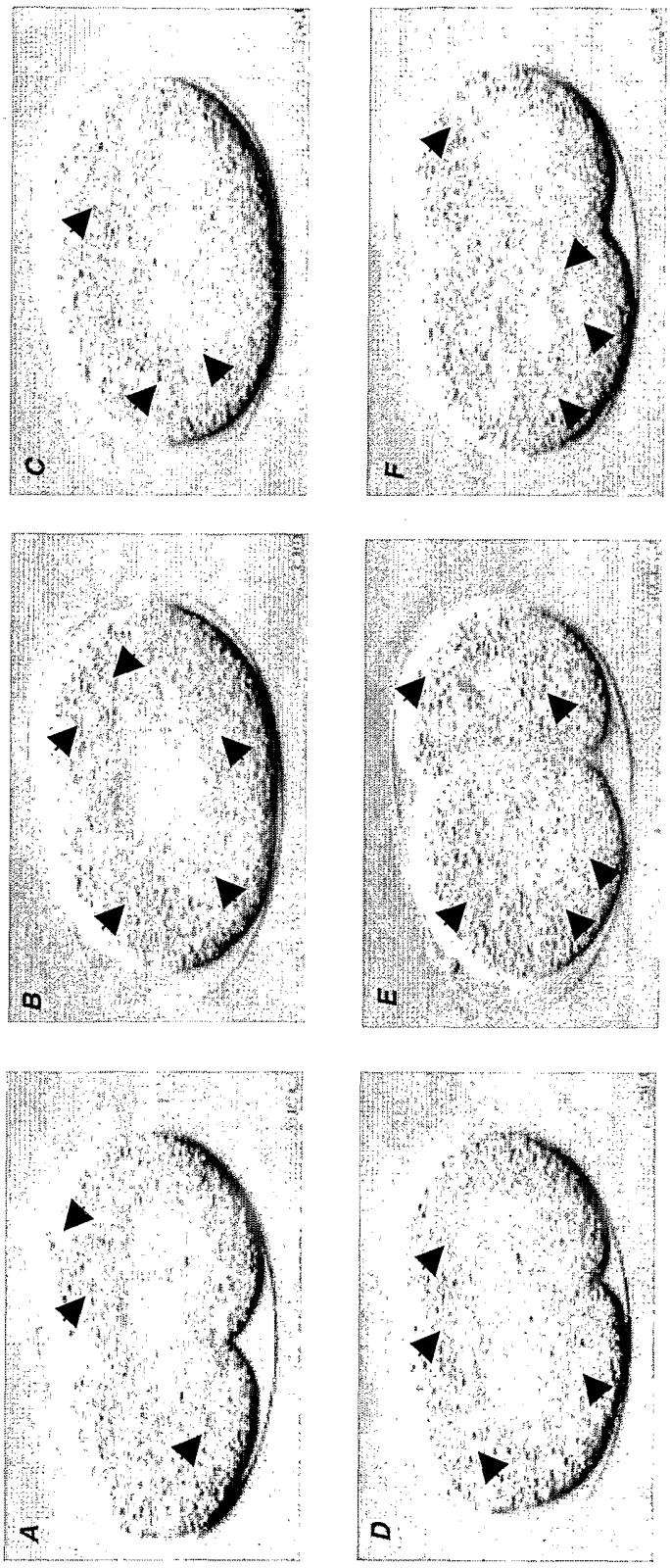

Fig. 10

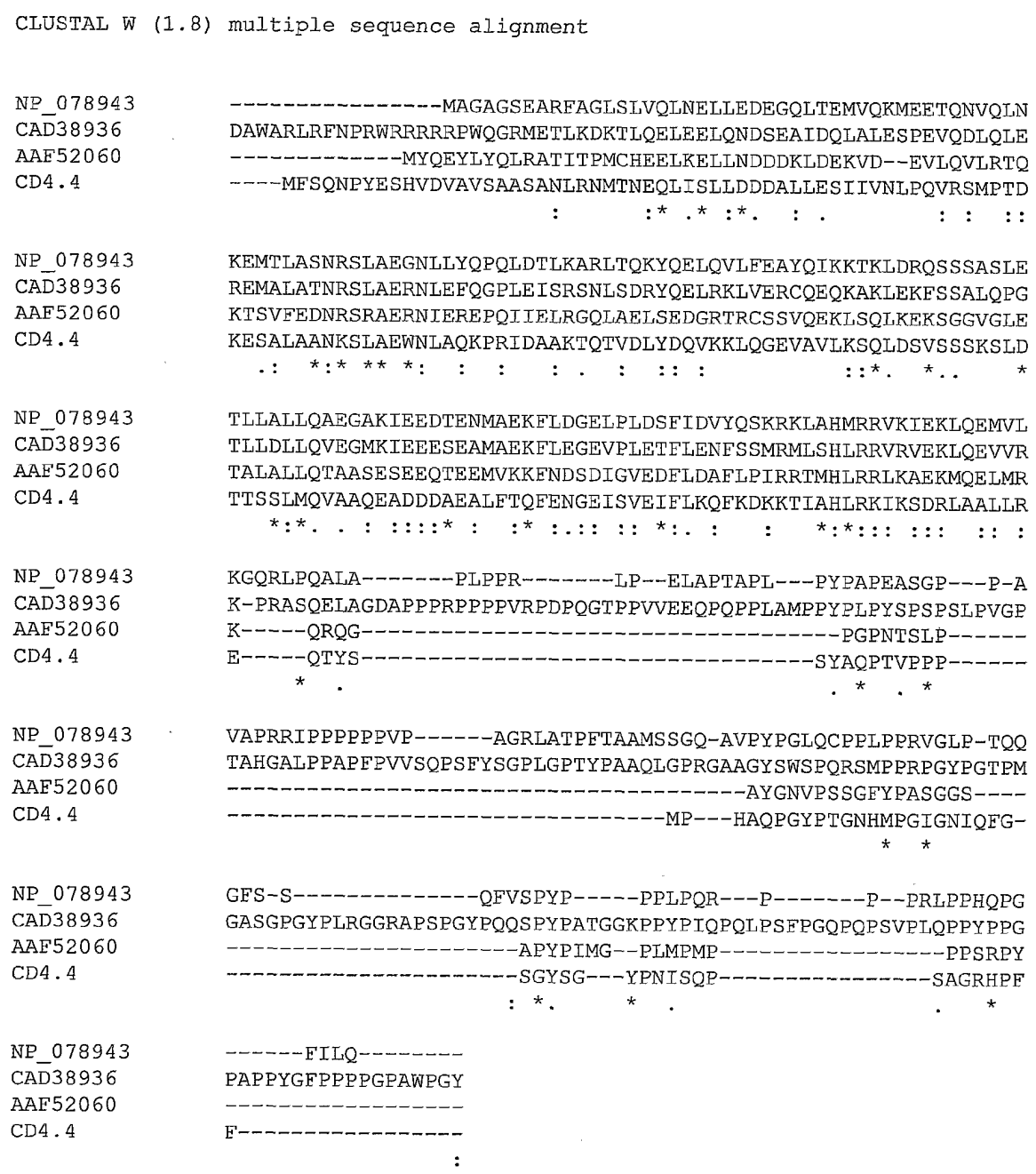
CLUSTAL W (1.8) multiple sequence alignment
NP_078943 ----------MAGAGSEARFAGLSLVQLNELLEDEGQLTEMVQKMEETQNVQLN
CAD38936 DAWARLRFNPRWRRRRRPWQGRMETLKDKTLQELEELQNDSEAIDQLALESPEVQDLQLE
AAF52060 ----------MYQEYLYQLRATITPMCHEELKELLNDDDKLDEKVD--EVLQVLRTQ
CD4.4 ----MFSQNPYESHVDVAVSAASANLRNMTNEQLISLLDDDALLESIIVNLPQVRSMPTD
NP_078943 KEMTLASNRSLAEGNLLYQPQLDTLKARLTQKYQELQVLFEAYQIKKTKLDRQSSSASLE
CAD38936 REMALATNRSLAERNLEFQGPLEISRSNLSDRYQELRKLVERCQEQKAKLEKFSSALQPG
AAF52060 KTSVFEDNRSRAERNIEREPQIIELRGQLAELSEDGRTRCSSVQEKLSQLKEKSGGVGLE
CD4.4 KESALAANKSLAEWNLAQKPRIDAAKTQTVDLYDQVKKLQGEVAVLKSQLDSVSSSKSLD
NP_078943 TLLALLQAEGAKIEEDTENMAEKFLDGELPLDSFIDVYQSKRKLAHMRRVKIEKLQEMVL
CAD38936 TLLDLLQVEGMKIEEESEAMAEKFLEGEVPLETFLENFSSMRMLSHLRRVRVEKLQEVVR
AAF52060 TALALLQTAASESEEQTEEMVKKFNDSDIGVEDFLDAFLPIRRTMHLRRLKAEKMQELMR
CD4.4 TTSSLMQVAAQEADDDAEALFTQFENGEISVEIFLKQFKDKKTIAHLRKIKSDRLAALLR
NP_078943 KGQRLPQALA-------PLPPR--------LP--ELAPTAPL---PYPAPEASGP---P-A
CAD38936 K-PRASQELAGDAPPPRPPPPVRPDPQGTPPVVEEQPQPPLAMPPYPLPYSPSPSLPVGP
AAF52060 K-----QRQG-----------------------------------PGPNTSLP------
CD4.4 E-----QTYS-----------------------------------SYAQPTVPPP------
NP_078943 VAPRRIPPPPPPVP------AGRLATPFTAAMSSGQ-AVPYPGLQCPPLPPRVGLP-TQQ
CAD38936 TAHGALPPAPFPVVSQPSFYSGPLGPTYPAAQLGPRGAAGYSWSPQRSMPPRPGYPGTPM
AAF52060 ----------AYGNVPSSGFYPASGGS----
CD4.4 ----------MP---HAQPGYPTGNHMPGIGNIQFG-
NP_078943 GFS-S----------QFVSPYP-----PPLPQR---P--------P--PRLPPHQPG
CAD38936 GASGPGYPLRGGRAPSPGYPQQSPYPATGGKPPYPIQPQLPSFPGQPQPSVPLQPPYPPG
AAF52060 ----------APYPIMG--PLMPMP----------PPSRPY
CD4.4 ----------SGYSG---YPNISQP----------SAGRHPF
NP_078943 ------FILQ--------
CAD38936 PAPPYGFPPPPGPAWPGY
AAF52060 ----------
CD4.4 F----------

Fig. 11

ZK546.1

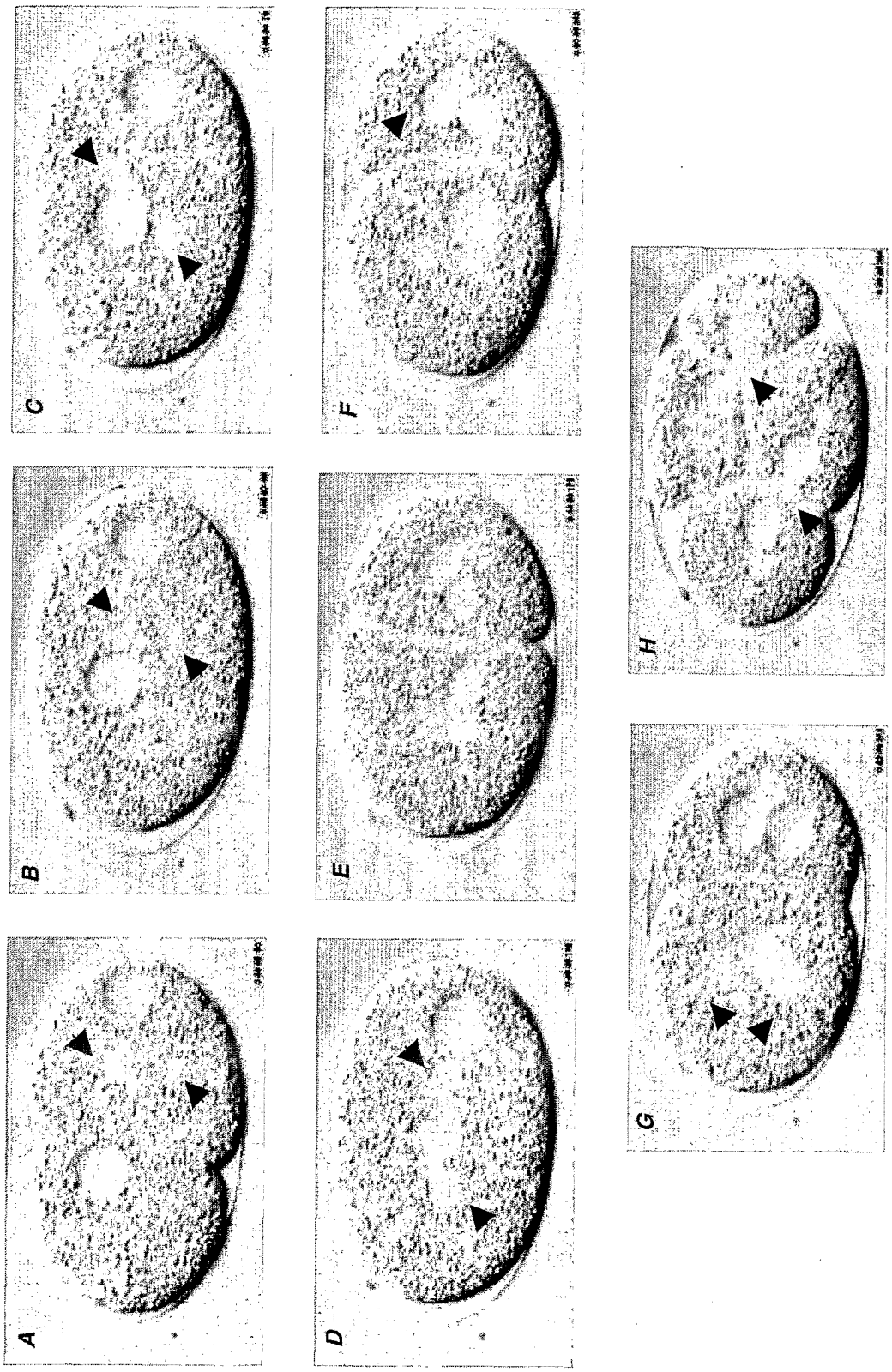

Fig. 12 1/7

CLUSTAL W (1.8) multiple sequence alignment

```
NP_056972       ------------------------------------------------------------
AAA74950        ---MAQQAADKYLYVDKNFINNPLAQADCGAKK-LVWVPSTKNGFEPASLKEEVGEEAIV
ZK546.1         ------------------------------------------------------------
NP_010225       ------------MDIIQGLIQQPKIQSVDETIP-TLCDRVENSTLISDRRSAVLGLKAFS
AAF53605        MSDDTSASGGTSAPFPSPVTADPEPGATASKLPGPIRSNIPTPATSGTGIPQPSKMKAPS
XP_109474       ------------------------------------------------------------

NP_056972       ------------------------------------------------------------
AAA74950        ELVENGKKVKVNKDDIQKMNPPKFSKVEDMAELTCLNEASVLHNLKERYYSGLIYTYSGL
ZK546.1         ------------------------------------------------------------
NP_010225       RQYRESVIASGLKPLLNTLKRDYMDEDSVKAILETILILFIRGDGHDDLTRGWISQQS-R
AAF53605        SFGSTGSVSKIGRPCCNHTTPKSGPPPREATSMSRESDDNLSSINSAYTDNSSAVLTANT
XP_109474       ----------------------------------MAQSRRHMSSRTPSGSRMSTEASAR

NP_056972       ------------------------------------------------------------
AAA74950        FCVVINPYKNLPIYSEEIVDMYKGKKRHEMPPHIYAITDTAYRSMMQDREDQSILCTGES
ZK546.1         ------------------------------------------------------------
NP_010225       LQNGKYPSPLVMKQEKEQVDQFSLWIADALTQSEDLIHLLVEFWEIDNFHIRLYTIQLLE
AAF53605        EQFIIGQRVWLGGTRPGQIAFIGDTHFAAGEWAGVVLDEPNGKNDGCVSGKRYFQCEPKR
XP_109474       PLRVGSRVEVIGKGHRGTVAYVGATLFATGKWVGVILDEAKGKNDGTVQGRKYFTCDEGH

NP_056972       ------------------------------------------------------------
AAA74950        GAGKTENTKKVIQYLAHVASSHKSKKDQGELERQLLQANPILEAFGNAKTVKNDNSSRFG
ZK546.1         ------------------------------------------------------------
NP_010225       AVMATRPLKARSALISLPTSISTMVSLLDDMHEPIRDEAILLLMAVVNDSPHVQKLVAFE
AAF53605        GIFSRLTRLTTYPLAGAQTPTSPLAKSSPDRSRTVSPTASIRSSMLRSPGIGGKNGMAVG
XP_109474       GIFVRQSQIQVFEDGADTTSPETPDSSASKVLK------------------------

NP_056972       ------------------------------------------------------------
AAA74950        KFIRINFDVNGYIVGANIETYLLEKSRAIRQAKEERTFHIFYYLLSGAGEHLKTDLLLEP
ZK546.1         ------------------------------------------------------------
NP_010225       NIFERLFSIIEEEGGLRGSLVVNDCLSLINNILKYNTSNQTLFLETGNLPKLAHLLSEPI
AAF53605        ----DRVIVSSGFGSRPGILRYLGETQFAPGNWCGVELDEPSGKNDGTVDDIRYFECKPK
XP_109474       ------------------------------------------REGADAAAKTSKLRGL
```

Fig. 12 2/7

```
NP_056972       ------------------------------------------------------------
AAA74950        YNKYRFLSNGHVTIPGQQDKDMFQETMEAMRIMGIPEDEQMGLLRVISGVLQLGNIVFKK
ZK546.1         ------------------------------------------------------------
NP_010225       SQDEVFFWNDQRIVNINTALDIVSLTVEPGNTVTTKHQNALLDSSVLMVVLRLAFFHNIP
AAF53605        YGVFVPIAKVSLSPSSKKTRLSRTGSRESLTSIGTMNSIATTATSRMRMNAQQRKSSTPV
XP_109474       KPKKAPTARKTTTRRPKPTRPASTGVAGPSSSLGPSGSASAGELSSSEPSTPAQTPLAAP


NP_056972       ------------------------------------------------------------
AAA74950        ERNTDQASMPDN----TAAQKVSHLLGINVTDFTRGILTPRIKVGRDYVQKAQTKEQADF
ZK546.1         ------------------------------------------------------------
NP_010225       KKVRPVALLTAANMVRSNEHAQLEFSKIDVPYFDPSLPVNSTANGGPIKLIPVVSILINW
AAF53605        KPILATPKSQFS-MQDLLREKQQHVEKLMVERDLDREDAQNQALQLQKNINELKARIVEL
XP_109474       IIPTPALTSPGAAPPLPSPSKEEEGLRAQVRDLEEKLETLRLKRSEDK---AKLKELEKH


NP_056972       ------------------------------------------------------------
AAA74950        AIEALAKATYERMFRWLVLRINKALDKTKRQGASFIGILDIAGFEIFDLNSFEQLCINYT
ZK546.1         ---------------------------------------------MLDLTNKESESSDNG
NP_010225       MLYANSVHTFDTRVACSRLLKAYFMDNFDLQRDFLLKQVQLCNNSTNNVGDNAKENGGSN
AAF53605        ESALDNERKKTEELQCSIDEAQFCGDELNAQSQVYKEKIHDLESKITKLVSATPSLQSIL
XP_109474       KIQLEQVQEWKSKMQEQQADLQRRLKEARKEAKEALEAKERYMEEMADTADAIEMATLDK


NP_056972       -------------------------------------------MEETQPPP----------
AAA74950        NEKLQQLFNHTMFILEQEEYQREGIEWNFIDFGLDLQPCIDLIEKPAGPPGILAL---LD
ZK546.1         NSKYEDSID----------------------GREVGTSKPFKEERSLED----------
NP_010225       KSDKESDSD-------KDTDGKDGTEYEGSFKANLFEVLLNYDAELNLNPFKLFFTTDIF
AAF53605        PPDLPSDDG-----ALQEEIAKLQEKMTIQQKEVESRIAEQLEEEQRLREN---------
XP_109474       EMAEERAES----------------------LQQEVEALKERVDELTTDL----------
                                                          :


NP_056972       ----QPKLPLCDSLMIWLQTFNTASPCQD----------VKQLTSGVAMAQVLHQIDAAW
AAA74950        EECWFPKATDKSFVEKVVQEQGTHPKFQK----------PKQLKDKADFCIIHYAGKVDY
ZK546.1         -----LQADLADMAVWMEGLDATKLPLND----------PQLLCNGRAFSEVLHNVDKNF
NP_010225       MFFFQQDHKYSEELREITRNVTTGNDLEDEEPLKAIQTISELLTTSLTAADIRIPISYLT
AAF53605        --VKYLNEQIATLQSELVSKDEALEKFSLSECG------IENLRRELELLKEENEKQAQE
XP_109474       ---EILKAEIEEKGSDGAASSYQLKQLEE----------QNARLKDALVRMRDLSSSEK
                                                        .
```

Fig. 12 3/7

```
NP_056972       FNESWLSRIKEDVGDNWR------------------------------------------
AAA74950        KADEWLMKNMDPLNDNIATLLHQSSDKFVSELWKDVDRIIGLDQVAGMSETALPGAFKTR
ZK546.1         FTDGWLETMPENRTTNIMVFR---------------------------------------
NP_010225       FLIYWLFGDFKATNDFLSDKS---------------------------------------
AAF53605        AQAEFTRKLAEKSVEVLRLSS---------------------------------------
XP_109474       QEHVKLQKLMEKKNQELEVVR---------------------------------------
                          .

NP_056972       ---------------------IKASN---------------------------VKKVLQ
AAA74950        KGMFRTVGQLYKEQLAKLMATLRNTNPNFVCCIIPNHEKKAGKLDPHLVLDQLRCNGVLE
ZK546.1         ------------------------------------------------------SCTRKLW
NP_010225       ----------VIKSLLSFSYQIQDEDVTIKCLVTMLLGVAYEFSSKESPFPRKEYFEFIT
AAF53605        ----------ELQNLKATSDSLESERVN---------------------KTDECEILQT
XP_109474       ------------------------------------------------QQRERLQE

NP_056972       GIM--SYYHEFLGQQISEALIPDLNQITECSDPVELG----------------------
AAA74950        GIR--ICRQGFPNRVVFQEFRQRYEILTPNSIPKGFMDGKQACVLMIKALELDSNLYRIG
ZK546.1         RKM--FDYVNHINRTVVSSRWTDIHERIDGIYESDLP----------------------
NP_010225       KTLGKDNYASRIKQFKKDSYFSKVDMNEDSILTPELDETG--------------------
AAF53605        EVRMRDEQIRELNQQLDEVTTQLNVQKADSSALDDMLRLQ--------------------
XP_109474       ELSQAESTIDELKEQVDAALGAEEMVEMLTDRNLNLEEKVR--------------------
                          .                    :

NP_056972       --------------------RLLQLILGCAINCE---------KKQEHIQNIMTLEES--
AAA74950        QSKVFFRSGVLAHLEEERDLKITDVIIGFQACCRGYLARKAFAKRQQQLTAMKVLQRNCA
ZK546.1         --------------------AMVNLGMAVVTLAHIG-------KNAKRFVDYSKALTS--
NP_010225       ----LPKVYFSTYFIQLFNENIYRIRTALSHDPDEEPINKISFEEVEKLQRQCTKLKG--
AAF53605        ----KEGTEEKSTLLEKTEKELVQSKEQAAKTLNDKEQLEKQISDLKQLAEQEKLVREMT
XP_109474       --------------------ELRETVGDLEAMNEMN-------DELQENARETELELR--
                                    :                    .  :.

NP_056972       ------------------------------------VQHVVMTAIQELMSKEILSSP
AAA74950        AYLRLRNWQWWRLFTKVKPLLNSIRHEDELLAKEAELTKVREKHLAAENRLTEMETMQSQ
ZK546.1         ------------------------------------THKSMMSNVAKMVTTVIDEMP
NP_010225       -----------------EITSLQTETESTHENLTEKLIALTNEHKELDEKYQILNSSHSS
AAF53605        EN---------------AINQIQLEKESIEQQLALKQNELEDFQKKQSESEVHLQEIKAQ
XP_109474       ---------------------------------EQLDMAGARVREAQKRVEAAQETVAD
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Fig. 12 4/7

```
NP_056972       PNDAVGELEQQLKR------ALEELQEALAEK-EELRQRCEELDMQVTTLQDEKNSLVSE
AAA74950        LMAEKLQLQEQLQAKTELCAEAEELRARLTAKKQELEEICHDLEARVEEEEERCQYLQAE
ZK546.1         ENPCFHEISELHGSQSELN-SLSESSGKLNGN--GSSERRSNADQILVDAELEIERLRTE
NP_010225       LKENFSILETELKNVRDSLDEMTQLRDVLETKDKENQTALLEYKSTIHKQEDSIKTLEKG
AAF53605        NTQKDFELVESGESLKKLQQQLEQKTLGHEKLQAALEELKKEKETIIKEKEQELQQLQSK
XP_109474       YQQTIKKYRQLTAHLQDVNRELTNQQEASVERQQQPPPETFDFKIKFAETKAHAKAIEME
                                     :                  : .  .   :   : :

NP_056972       NEMMNEKLDQLDGSFDD---PNTVVAKKYFHAQLQLEQLQEE--------NFRLEAAKDD
AAA74950        KKKMQQNIQELEEQLEEEESARQKLQLEKVTTEAKLKKLEEDQI-IMEDQNCKLAKEKKL
ZK546.1         TENQRKEIERLTKSFET---AQHDMSSNSESGDISILEKQNEE---LRQKRRELEEKNLE
NP_010225       LETILSQKKKAEDGINKMGKDLFALSREMQAVEENCKNLQKEKDKSNVNHQKETKSLKED
AAF53605        SAESESALKVVQVQLEQLQQQAAASGEEGSKTVAKLHDEISQLKSQAEETQSELKSTQSN
XP_109474       LRQMEVAQANRHMSLLTAFMPDSFLRPGGDHDCVLVLLLMPR-LICKAELIRKQAQEKFD
                              :                                        .    :

NP_056972       YRVHCEELEKQLIEFQHRNDELTSLAEETRALKDEIDV----LRATS----DKANKLEST
AAA74950        LEDRVAEFTTDLMEEEEKSKSLAKLKNKHEAMITDLEER---LRREE----KQRQELEKT
ZK546.1         LDAAVDQFKGIVFELTNENDVLRRSDKERQRLQTVLDAAQSDLDEWK----TVANQYQKE
NP_010225       IAAKITEIKAINENLEEMKIQCNNLSKEKEHISKELVEYKSRFQSHDNLVAKLTEKLKSL
AAF53605        LEAKSKQLEAANGSLEEEAKKSGHLLEQITKLKSEVGETQAALSSCHTDVESKTKQLEAA
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AAA74950        RRKLEGDSTDLSDQIAELQAQIAELKMQLAKKEEELQAALARVEEEAAQKNMALKKIREL
ZK546.1         AELSKQQDKEIKELLSQNKALKSRLDHHVKS--------ATLEDANKNGIAQLRTQVGGL
NP_010225       ANNYKDMQAENESLIKAVEESKNESSIQLSNLQNKIDSMSQEKENFQIERGSIEKNIEQL
AAF53605        NAALEKVNKEYAESRAEASDLQDKVKEITDT-------LHAELQAERSSSSALHTKLSKF
XP_109474       MSAHERSLDFLIELLHKDQLDETVNVEPLTK---------AIKYYQHLYSIHLAEQPEDS
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NP_056972       KRQVQDLHVKLSSE-------------------------------------SKR----
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NP_010225       KKTISDLEQTKEEIISKSDSSKDEYESQISLLKEKLETATTANDENVNKISELTKTREEL
AAF53605        SDEIATGHKELTSKADAWS-----------------------------QEMLQKEKEL
XP_109474       TMQLADHIKFTQSALD-----------------------------------------CM
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Fig. 12 5/7

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NP_056972       ----------ADTLAFEMKRLEEKHEALLKEKERLIEQRDTLKETNEELRCSQVQQD---
AAA74950        SILKKTLEDEAKTHEAQIQEMRQKHSQAVEELAEQLEQTKRVKATLEKAKQTLENERGEL
ZK546.1         ---------CVEQLEIQLIQHKEKVKELEDRKDELIEERNRLENQLIFKEAVTPRS----
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AAF53605        QELRQQLQDSQDSQTKLKAEGERKEKSFEESIKNLQEEVTKAKTENLELSTGTQTTIKD-
XP_109474       G--------VEVGRLRAFLQGGQEATDIALLLRDLETSCSDTRQFCKKIRRRMPGTDAPG
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ZK546.1         ------------------------------------------------------------LH
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AAF53605        ----------------------LQERLEITNAELQHKEKMASEDAQKIADLKTLVEAI
XP_109474       ------------------------------------------------IPAALAFG
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NP_056972       NQTDASATKSYENLAAEIMPVEYREVFIR----------------LQHENKM------LR
AAA74950        NQSDSKSSKLTKDFSALESQLQDTQELLQEENRQKLSLS-TKLKQMEDEKNS------FR
ZK546.1         ESMFEAGNLSFEPFS------EKNTLP-----------------LEIENK--------R
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AAF53605        QVANANISATNAELSTVLEVLQAEKSETNHIFELFEMEADMNSERLIEKVTGIKEELKET
XP_109474       SQVSDTLLDCRKHLTWVVAVLQEVAAAAAQLIAPLAENEGLPVAALEELAFKAS-----E
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AAF53605        HLQLDERQKKFEELEEKLKQAQQSEQKLQQESQ-------TSKEKLTEIQQSLQELQDSV
XP_109474       QIYGSPSSSPYECLRQSCTILISTMNKLATAMQEGEYDAERPPSKPPPVELRAAALRAEI
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AAF53605        KQKEELVQNLEEKVRE----------------------------------S---SSIIE
XP_109474       TDAEG---------------------------------------------------------
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Fig. 12 6/7

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NP_056972       -QGSKSEGESSSK-------------------------------------------------
AAA74950        EERDRAEAEAREKETKALSLARALEEAMEQKA-----ELERLNKQFRTEMEDLMSSKDDV
ZK546.1         -NQEHASGDVVG-------------------------------------------------
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AAF53605        AQNTKLNESNVQLENKTSCLKETQDQLLES-------QKK--EKQLQEEAAKLSGELQQV
XP_109474       -LGLKLEDRETVIK-----------------------------------------------
                   : .

NP_056972       -------------LKQKLEAHMEKLTEVHEELQK---------------KQELIEDLQPD
AAA74950        GKSVHELEKSNRALEQQVEEMKTQLEELEDELQATEDAKLRLEVNLQAMKAQFERDLQGR
ZK546.1         -------------LKIQLEKAEVEAQQMREAKMRAETN-----------QAQVDEILKKR
NP_010225       SEKINTLEDELIRLQNENELKAKEIDNTRSELEKVSLSNDELLEEKQNTIKSLQDEILSY
AAF53605        QEANGDIKDSLVKVEELVKVLEEKLQAATSQLDAQQATN-KELQELLVKSQENEGNLQGE
XP_109474       -------------ELKKSLKIKGEELSEANVRLSLLEKKLDS-------AAKDADERIEKV
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NP_056972       INQN-------VQKINELEAALQ--------------KKDEDMKAMEERYKMYLEKARNV
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ZK546.1         TAELEVN----ATALQKAKAVID--------------ELEYNSRPVSEDSMTSVQAFKEM
NP_010225       KDKITRNDEKLLSIERDNKRDLESLKEQLRAAQESKAKVEEGLKKLEEESSKEKAELEKS
AAF53605        SLAVTEKLQQLEQANGELKEALCQKENGLKELQG---KLDESNTVLESQKKSHNEIQDKL
XP_109474       QTRLDETQTLLRKKEKDFEETMD--------------ALQADIDQLEAEKAELKQRLNSQ
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NP_056972       ----------------------------RRIEILESECKVAKFRDYEEKLIVSAWYNKS-
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NP_010225       ----------------------------EKLEQSKKSAEEDIKNLQHEKSDLISRINESE
AAF53605        ----------------------------EELQKSLQQKQLLLEKGNEFDTQLAEYQKVID
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NP_056972       LAFQKLGMESRLVSGGGACSDTGACTPA----------RSFLAQQRHITNTRRNLSVKVP
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ZK546.1         TLLDTQKMSGALPWRSLASETRRELPTA----------MASILVLGFLVFIAWMFININS
NP_010225       KDIEELKSKLRIEAKSGSELETVKQELNNAQEKIRINAEENTVLKSKLEDIERELKDKQA
AAF53605        EMDDAASVKSALLEQLQNRVAELETALRQANDAQKTAYLETKELRRQLESLELEKSREVL
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AAA74950        ASIAALEAK------------IAQLEEQLDNETKERQAASKQVRRAEKKLKDVLLQVED
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XP_109474       QVAQLKSLSDTIEKLKDEVLKETVTQRPGATVPTDFATFPSSAFLRAKEEQQDDTVYMGK


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ZK546.1         ---------------------------------------------
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AAF53605        QDYSTPSSESNNNEKERKLPAPRKYCDSCEVFGHDTSECADDETY--
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Fig. 13

C56C10.3

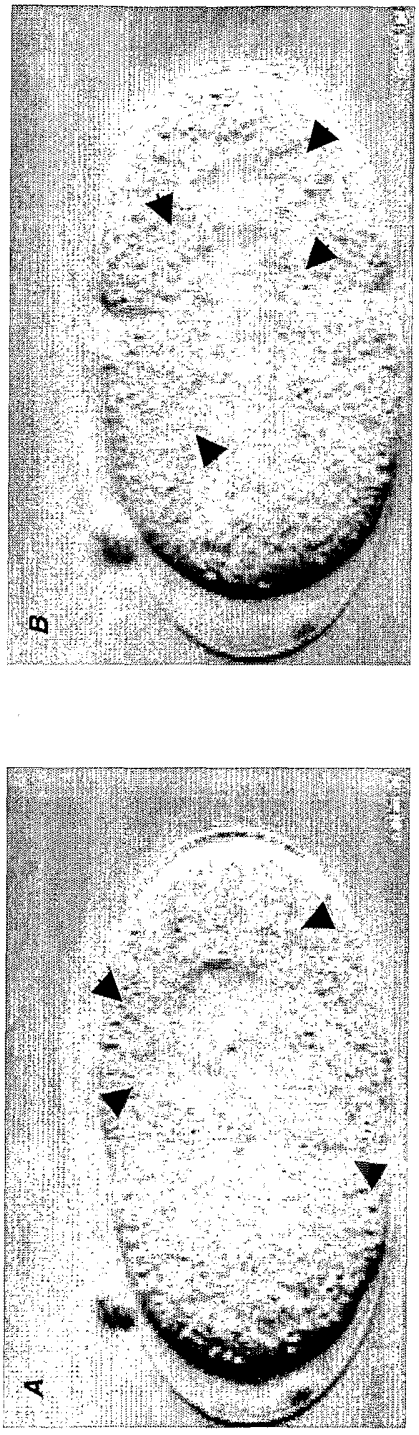

Fig. 14

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CLUSTAL W (1.8) multiple sequence alignment for C56C10.3


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C56C10.3        MSLFGKIF---GGRKQEAPSTPQESIQKLRETEEMLEKKQEFLEKKVIDEKQNAVKYGTK
AAF58977        MSFFGKMF---GGKK-EVAPTTGEAIQKLRETENMLIKKQEFLEAKIEDELNIARKNASK
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NP_083638       NKRAALQALKRKKRYEKQLAQIDGTLSTIEFQREALENANTNTEVLKNMGYAAKAMKAAH
C56C10.3        NKRMALQCLNRKRNFEKQLAHIDGVLSTIGYQREALENASTNAEVLNVMGTASKALKAAH
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XP_059282       DNMDIDKVDELMQDIADQQELAEEISTAISKPVGFGEEFDEDELMAELEELEQEELDKNL
NP_083638       DNMDIDKVDELMQDIADQQELAEEISTAISKPVGFGEEFDEDELMAELEELEQEELDKNL
C56C10.3        NNMDIDQVHDLMEDIAEQQEVANEIAEAISNPVGFSTAVDDDDLMRELEALEQEELDKEL
AAF58977        QNMDVDKVHDMMDDIAEQQDVAREISDAISNPVAFGADLDDEDLERELDELEQENFDKEI
                ***:*:*.::*:***:**::*.**: ***:**.*.  .*:::*  **: ****::**:::

XP_059282       LEISGPETVPLPNVPSIALPSKPAKK---------KEEEDDDMKELENWAGSM
NP_083638       LEISGPETVPLPNVPSVALPSKPAKK---------KEEEDDDMKELENWAGSM
C56C10.3        LDARAP-PVTLPDTPNIALPAVPASRP-------RAKEADKDLEDLESWANA-
AAF58977        IGIPEP-TPTLPEAPTEDLPEKAKEKKKATTTTAVEDDDDPDMKQLLSWSN--
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Fig. 15

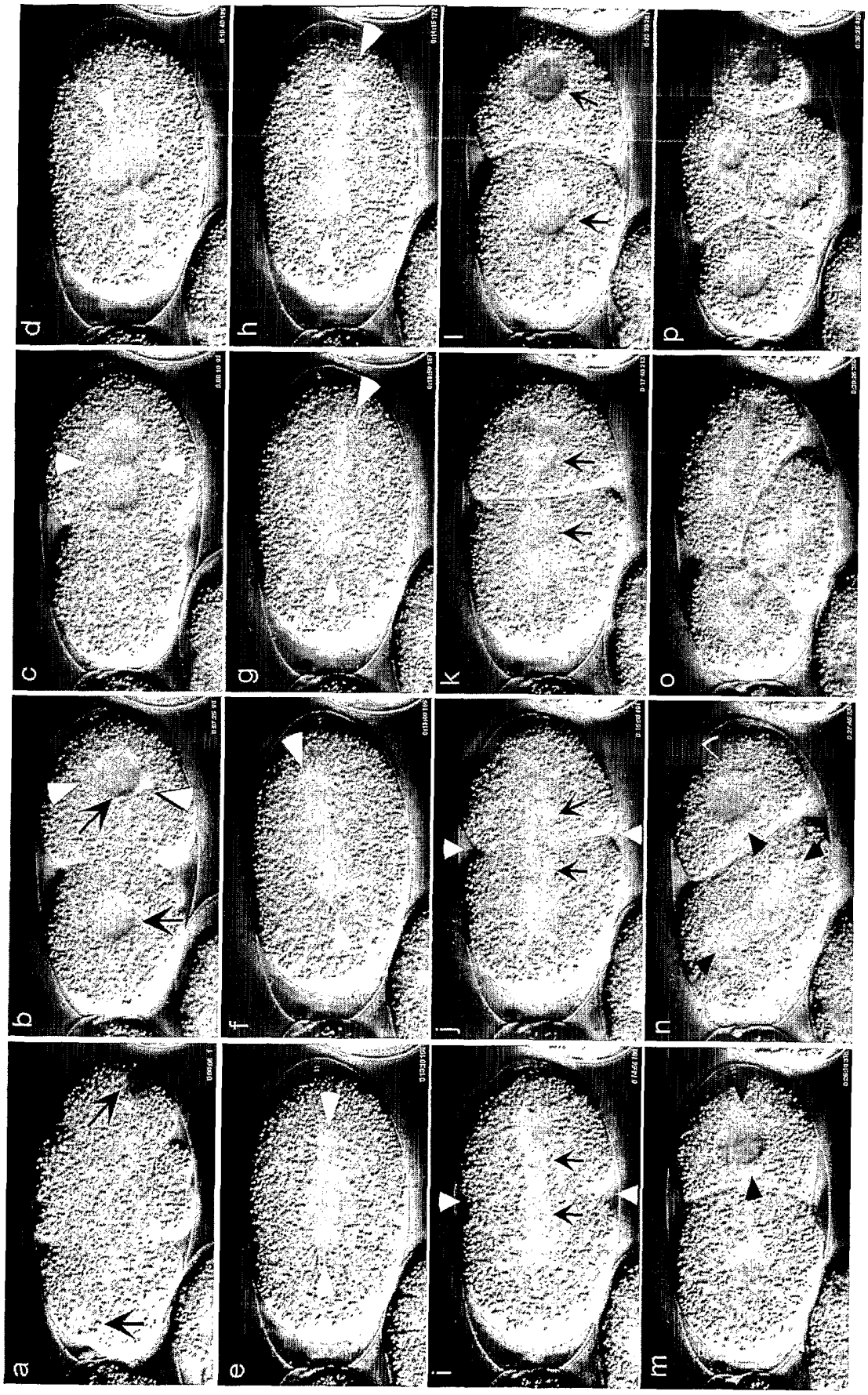

Fig.16

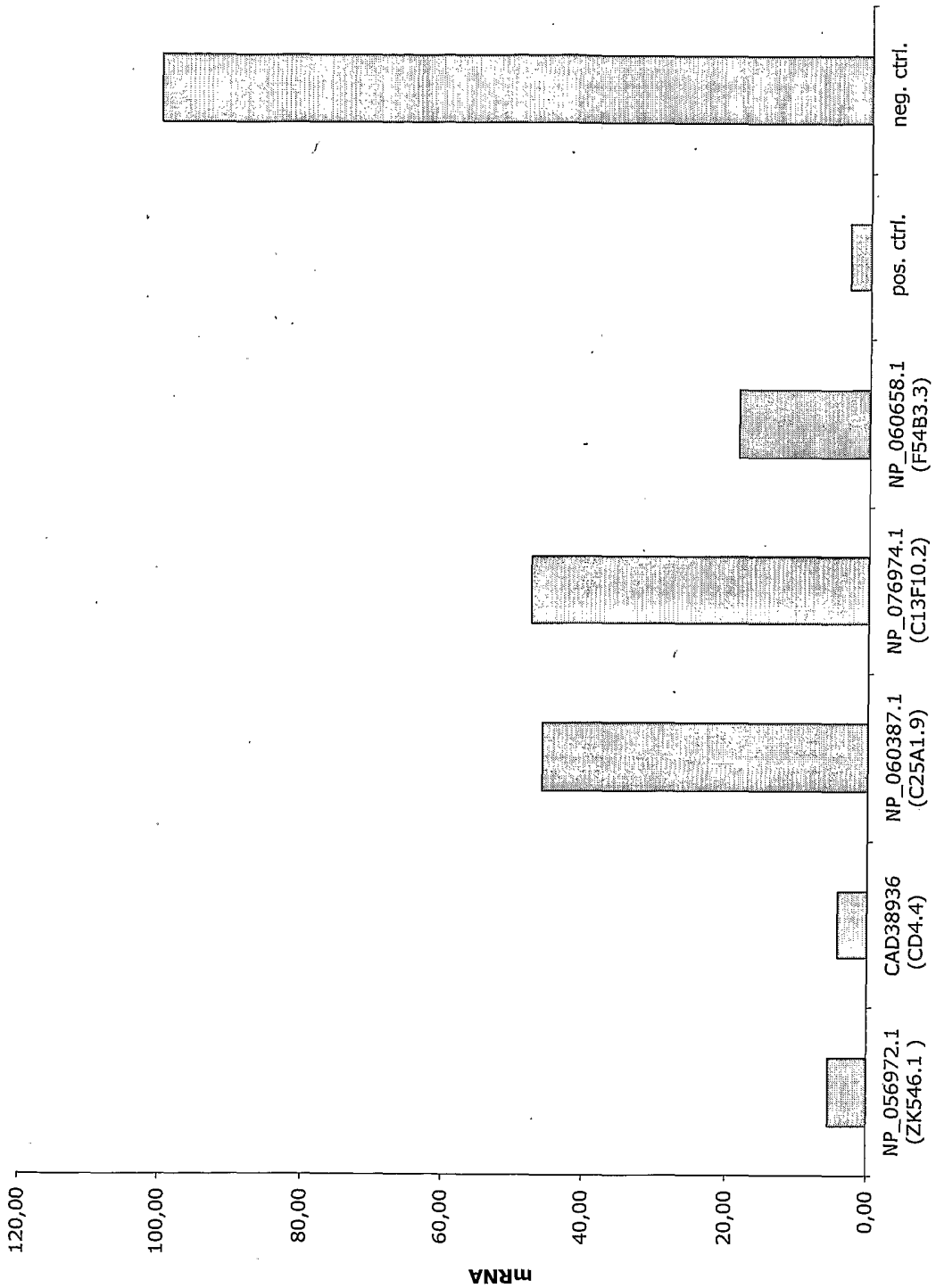
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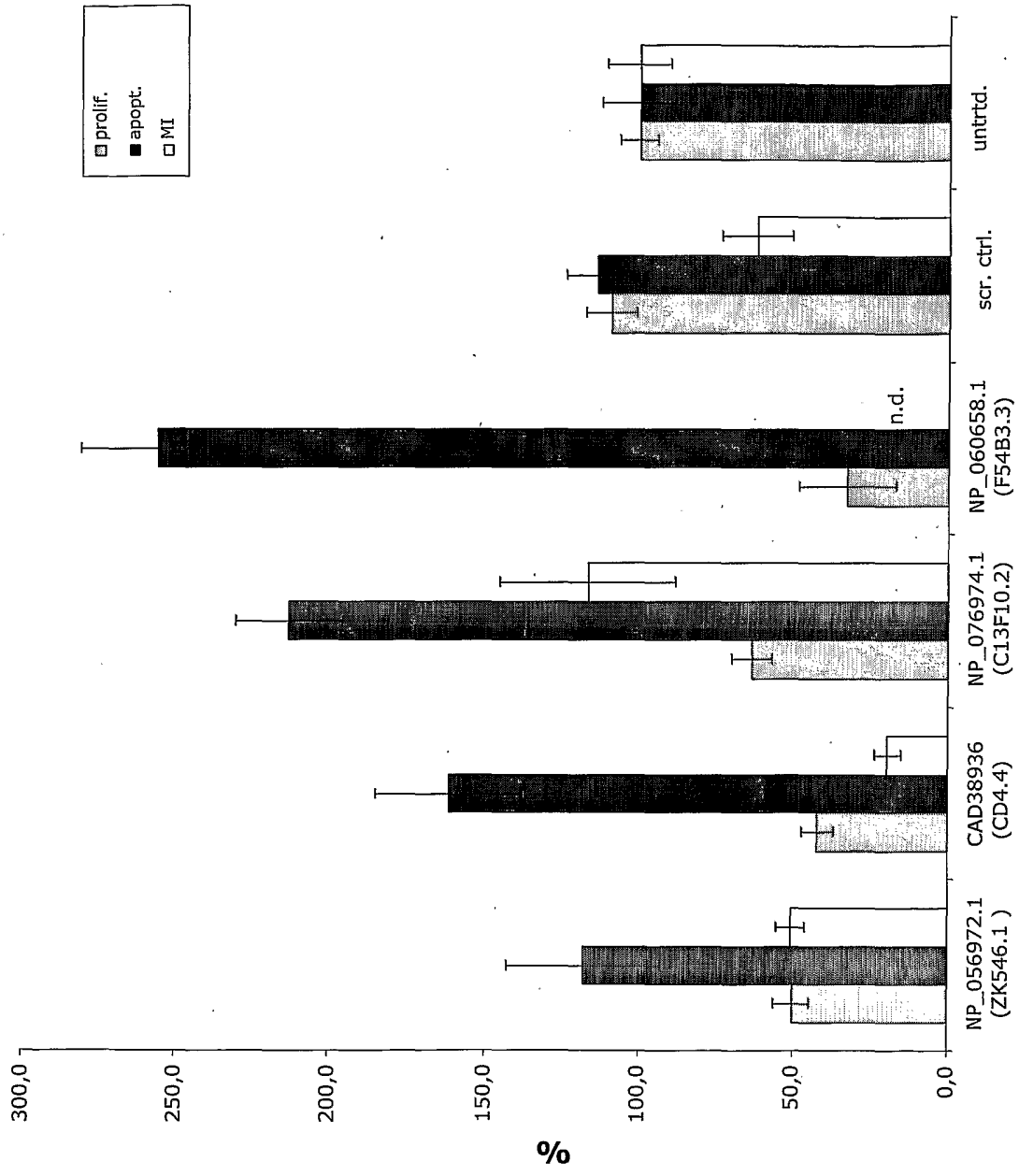
Fig. 17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Asp Phe Val Ala Thr His Phe Ile Pro Ile Met Ile Glu Glu Pro Glu
                165                 170                 175

Asn Pro Val Tyr Tyr Thr Ala Tyr Ala Val Gly Thr Ile Phe Phe Leu
            180                 185                 190

Leu Gly Ala Arg Arg Arg Asp Cys Val Tyr Leu Lys Asp Leu Leu Ala
        195                 200                 205

Ser Thr Leu Leu Leu Gln Leu Glu Glu Cys Ile His Ala Glu Asn His
    210                 215                 220

Cys Leu Ser Pro Pro Lys Ile Asp Val Phe Thr Val Ala Gln Phe Arg
225                 230                 235                 240
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Thr Thr Leu Ser Glu Phe Arg Phe Leu Asp Ser Gln Arg Lys Gly Leu
245 250 255

Leu Ala Pro Ala Asp Leu Lys Phe Phe Arg Asp Gly Ile Phe Asn Glu
260 265 270

Val Phe Thr Lys Arg Ile Phe Glu Ile Ser Ile Thr Tyr Glu Asp Gly
275 280 285

Arg Ile Asp Phe Lys Ala Phe Val Asp Phe Val Thr Ala Leu Lys Phe
290 295 300

Arg His Thr Thr Ala Ser Ala Lys Tyr His Phe Glu Ile Leu Asp Leu
305 310 315 320

Lys Asp Asp Gly Leu Leu Asp Glu Glu Glu Ile Arg Ser Ile Ser Ser
325 330 335

Phe Gln Leu Gln Asn Leu Pro Asp Tyr Val Pro Glu Asp Asn Ser Val
340 345 350

Asn Pro Glu Val Ala Thr Ala Glu Leu Arg Asp Met Met Arg Leu Asn
355 360 365

Gln Asn Gly Ile Thr Leu Glu Glu Phe Leu Ala Asn Arg Met Asn Ser
370 375 380

Thr Phe Ala Gly Phe Leu Ser Asn Ser Asp Asp Tyr Met Lys Tyr Glu
385 390 395 400

Arg Arg Glu Gln

<210> 9

<211> 1362

<212> DNA

<213> Homo sapiens

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gaatggaaag gaggtagaaa aaacacaaat gaattctata agaccattcc ccggttttat 180

tataggctgc ctgctgaaga tgaagtctta ctacagaaat taagagagga atcaagagct 240

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<210> 10

<211> 453

<212> PRT

<213> Homo sapiens

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Asp Leu Phe Thr Lys Tyr Tyr Ser Glu Trp Lys Gly Gly Arg Lys Asn
35 40 45

Thr Asn Glu Phe Tyr Lys Thr Ile Pro Arg Phe Tyr Tyr Arg Leu Pro
50 55 60

Ala Glu Asp Glu Val Leu Leu Gln Lys Leu Arg Glu Glu Ser Arg Ala
65 70 75 80

Val Phe Leu Gln Arg Lys Ser Arg Glu Leu Leu Asp Asn Glu Glu Leu
85 90 95

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Gln Asn Leu Trp Phe Leu Leu Asp Lys Arg Gln Thr Pro Pro Met Ile
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Gly Glu Glu Ala Met Ile Asn Tyr Glu Asn Phe Leu Lys Val Gly Glu
        115                 120                 125

Lys Ala Gly Ala Lys Cys Lys Gln Phe Phe Thr Ala Lys Val Phe Ala
    130                 135                 140

Lys Leu Leu His Thr Asp Ser Tyr Gly Arg Ile Ser Ile Met Gln Phe
145                 150                 155                 160

Phe Asn Tyr Val Met Arg Lys Val Trp Leu His Gln Thr Arg Ile Gly
                165                 170                 175

Leu Ser Leu Tyr Asp Val Ala Gly Gln Gly Tyr Leu Arg Glu Ser Asp
            180                 185                 190

Leu Glu Asn Tyr Ile Leu Glu Leu Ile Pro Thr Leu Pro Gln Leu Asp
        195                 200                 205

Gly Leu Glu Lys Ser Phe Tyr Ser Phe Tyr Val Cys Thr Ala Val Arg
    210                 215                 220

Lys Phe Phe Phe Phe Leu Asp Pro Leu Arg Thr Gly Lys Ile Lys Ile
225                 230                 235                 240

Gln Asp Ile Leu Ala Cys Ser Phe Leu Asp Asp Leu Leu Glu Leu Arg
                245                 250                 255

Asp Glu Glu Leu Ser Lys Glu Ser Gln Glu Thr Asn Trp Phe Ser Ala
            260                 265                 270

Pro Ser Ala Leu Arg Val Tyr Gly Gln Tyr Leu Asn Leu Asp Lys Asp
        275                 280                 285

His Asn Gly Met Leu Ser Lys Glu Glu Leu Ser Arg His Gly Thr Ala
    290                 295                 300

Thr Met Thr Asn Val Phe Leu Asp Arg Val Phe Gln Glu Cys Leu Thr
305                 310                 315                 320

Tyr Asp Gly Glu Met Asp Tyr Lys Thr Tyr Leu Asp Phe Val Leu Ala
                325                 330                 335

Leu Glu Asn Arg Lys Glu Pro Ala Ala Leu Gln Tyr Ile Phe Lys Leu
            340                 345                 350

Leu Asp Ile Glu Asn Lys Gly Tyr Leu Asn Val Phe Ser Leu Asn Tyr
        355                 360                 365
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Phe Phe Arg Ala Ile Gln Glu Leu Met Lys Ile His Gly Gln Asp Pro
370 375 380

Val Ser Phe Gln Asp Val Lys Asp Glu Ile Phe Asp Met Val Lys Pro
385 390 395 400

Lys Asp Pro Leu Lys Ile Ser Leu Gln Asp Leu Ile Asn Ser Asn Gln
405 410 415

Gly Asp Thr Val Thr Thr Ile Leu Ile Asp Leu Asn Gly Phe Trp Thr
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Tyr Glu Asn Arg Glu Ala Leu Val Ala Asn Asp Ser Glu Asn Ser Ala
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Asp Leu Asp Asp Thr
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<210> 11

<211> 1833

<212> DNA

<213> Caenorhabditis elegans

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<211> 610
<212> PRT
<213> Caenorhabditis elegans

<400> 12

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Asp Phe Gln Ala Gly Ala Ala Pro Gly Gly Pro Gln Gln Pro Gly Gln
35 40 45

Gly Gln Arg Gln Glu Gly Asn Ser Lys Met Ala Tyr Ser Phe Asp Ser
50 55 60

Thr Ala Leu Glu Arg Ala Ala Lys Ala Ala Arg Asp Leu Glu Lys Phe
65 70 75 80

Pro Asn Ala Lys Glu Ala Leu Glu Leu Ser Arg Met Gln Glu Val Thr
85 90 95

Arg Gln Lys Glu Val Glu Asn Glu Thr Lys Lys Ile Glu Ala Gln Leu
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Ala Asn Met Lys Ser Glu His Ile Arg Val Ala Glu Glu Glu Arg Arg
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Lys Thr Leu Gly Glu Glu Thr Lys His Ala His Ser Arg Ala Glu Tyr
    130                 135                 140

Gln Asp Gln Leu Ala Arg Lys Arg Ala Glu Glu Glu Leu Ala Met Lys
145                 150                 155                 160

Ala Arg Met Gln Glu Glu Ser Leu Arg Lys Gln Glu Glu Ser Val Lys
                165                 170                 175

Lys Gln Glu Gln Leu Arg Lys Gln Thr Ile Glu His Glu Leu Ala Leu
            180                 185                 190

Lys His Lys Tyr Glu Leu Glu Lys Ile Asp Ala Glu Thr Arg Ala Arg
        195                 200                 205

Ala Lys Ala Ala Arg Asp Asn Arg Asp Val Asn Leu Glu Gln Met Lys
    210                 215                 220

Leu His Glu Glu Glu Asn Arg Lys Thr Val Ile Glu Lys Ile Lys Thr
225                 230                 235                 240

Ser Gly Glu Leu Ile Gly Ser Gly Leu Asn Gln Phe Leu Asn Asp Lys
                245                 250                 255

Thr Lys Ile Ala Ala Ala Val Gly Gly Leu Thr Ala Leu Ala Val Gly
            260                 265                 270

Trp Tyr Thr Ala Lys Arg Gly Thr Gly Val Thr Ala Arg Tyr Ile Glu
        275                 280                 285

Ser Arg Leu Gly Lys Pro Ser Leu Val Arg Glu Thr Ser Arg Ile Thr
    290                 295                 300

Pro Leu Glu Val Leu Lys His Pro Ile Lys Ser Val Gln Met Met Thr
305                 310                 315                 320

Arg Gln Lys Lys Asp Pro Leu Asn Gly Val Val Leu Pro Pro Ala Leu
                325                 330                 335

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

Asn Asn Gly Leu Phe Arg Asn Val Met Phe Tyr Gly Pro Pro Gly Thr
        355                 360                 365

Gly Lys Thr Leu Phe Ala Lys Ser Leu Ala Gln His Ser Gly Leu Asp
    370                 375                 380
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Tyr Ala Val Leu Thr Gly Gly Asp Ile Ala Pro Leu Gly Arg Asp Gly
385 390 395 400

Val Ser Ala Ile His Lys Val Phe Asp Trp Ala Ser Lys Ser Arg Lys
405 410 415

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

Ser Lys Asn Gly Met Ser Glu Asp Thr Arg Ala Ala Leu Asn Ala Phe
435 440 445

Leu Phe Arg Thr Gly Glu Gln Ser Arg Lys Phe Met Leu Val Val Ala
450 455 460

Ser Asn Gln Pro Glu Gln Phe Asp Trp Ala Val Asn Asp Arg Phe Asp
465 470 475 480

Gln Leu Val Glu Phe Thr Leu Pro Gly Met Glu Glu Arg Glu Arg Ile
485 490 495

Leu Leu Gln Tyr Phe Asn Glu His Ile Val Thr Pro Ala Thr Ser Gly
500 505 510

Ser Arg Ser Gln Arg Leu Lys Leu Asp Asn Phe Asp Trp Val Ala Lys
515 520 525

Cys Asn Glu Val Ala Lys Lys Thr Ser Gly Met Ser Gly Arg Glu Leu
530 535 540

Ser Lys Leu Val Ile Gly Trp Gln Ala Ser Ala Tyr Ala Ser Glu Thr
545 550 555 560

Gly Val Leu Thr Glu Ala Ile Val Asp Arg Asn Thr Ala Asp Ala Met
565 570 575

Val Gln His Glu His Lys Met Glu Trp Leu Glu Lys Glu Gln Leu Lys
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Ala Arg Asn Gln Glu Val Lys Phe Gly Thr Thr Leu Lys Arg Glu Thr
595 600 605

Ala Val
610

<210> 13

<211> 1761

<212> DNA

<213> Homo sapiens

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<210> 14
<211> 586
<212> PRT

<213> Homo sapiens

<400> 14

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Gly Pro Pro Pro Pro Leu Pro Pro Ala Gln Pro Gly Ala Glu Gly Gly
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Gly Asp Arg Gly Leu Gly Asp Arg Pro Ala Pro Lys Asp Lys Trp Ser
        35                  40                  45

Asn Phe Asp Pro Thr Gly Leu Glu Arg Ala Ala Lys Ala Ala Arg Glu
    50                  55                  60

Leu Glu His Ser Arg Tyr Ala Lys Asp Ala Leu Asn Leu Ala Gln Met
65                  70                  75                  80

Gln Glu Gln Thr Leu Gln Leu Glu Gln Gln Ser Lys Leu Lys Glu Tyr
                85                  90                  95

Glu Ala Ala Val Glu Gln Leu Lys Ser Glu Gln Ile Arg Ala Gln Ala
            100                 105                 110

Glu Glu Arg Arg Lys Thr Leu Ser Glu Glu Thr Arg Gln His Gln Ala
        115                 120                 125

Arg Ala Gln Tyr Gln Asp Lys Leu Ala Arg Gln Arg Tyr Glu Asp Gln
    130                 135                 140

Leu Lys Gln Gln Gln Leu Leu Asn Glu Glu Asn Leu Arg Lys Gln Glu
145                 150                 155                 160

Glu Ser Val Gln Lys Gln Glu Ala Met Arg Arg Ala Thr Val Glu Arg
                165                 170                 175

Glu Met Glu Leu Arg His Lys Asn Glu Met Leu Arg Val Glu Ala Glu
            180                 185                 190

Ala Arg Ala Arg Ala Lys Ala Glu Arg Glu Asn Ala Asp Ile Ile Arg
        195                 200                 205

Glu Gln Ile Arg Leu Lys Ala Ala Glu His Arg Gln Thr Val Leu Glu
    210                 215                 220

Ser Ile Arg Thr Ala Gly Thr Leu Phe Gly Glu Gly Phe Arg Ala Phe
225                 230                 235                 240

Val Thr Asp Trp Asp Lys Val Thr Ala Thr Val Ala Gly Leu Thr Leu
                245                 250                 255
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Leu Ala Val Gly Val Tyr Ser Ala Lys Asn Ala Thr Leu Val Ala Gly
            260                 265                 270

Arg Phe Ile Glu Ala Arg Leu Gly Lys Pro Ser Leu Val Arg Glu Thr
        275                 280                 285

Ser Arg Ile Thr Val Leu Glu Ala Leu Arg His Pro Ile Gln Val Ser
    290                 295                 300

Arg Arg Leu Leu Ser Arg Pro Gln Asp Ala Leu Glu Gly Val Val Leu
305                 310                 315                 320

Ser Pro Ser Leu Glu Ala Arg Val Arg Asp Ile Ala Ile Ala Thr Arg
                325                 330                 335

Asn Thr Lys Lys Asn Arg Ser Leu Tyr Arg Asn Ile Leu Met Tyr Gly
            340                 345                 350

Pro Pro Gly Thr Gly Lys Thr Leu Phe Ala Lys Lys Leu Ala Leu His
        355                 360                 365

Ser Gly Met Asp Tyr Ala Ile Met Thr Gly Gly Asp Val Ala Pro Met
    370                 375                 380

Gly Arg Glu Gly Val Thr Ala Met His Lys Leu Phe Asp Trp Ala Asn
385                 390                 395                 400

Thr Ser Arg Arg Gly Leu Leu Leu Phe Val Asp Glu Ala Asp Ala Phe
                405                 410                 415

Leu Arg Lys Arg Ala Thr Glu Lys Ile Ser Glu Asp Leu Arg Ala Thr
            420                 425                 430

Leu Asn Ala Phe Leu Tyr Arg Thr Gly Gln His Ser Asn Lys Phe Met
        435                 440                 445

Leu Val Leu Ala Ser Asn Gln Pro Glu Gln Phe Asp Trp Ala Ile Asn
    450                 455                 460

Asp Arg Ile Asn Glu Met Val His Phe Asp Leu Pro Gly Gln Glu Glu
465                 470                 475                 480

Arg Glu Arg Leu Val Arg Met Tyr Phe Asp Lys Tyr Val Leu Lys Pro
                485                 490                 495

Ala Thr Glu Gly Lys Gln Arg Leu Lys Leu Ala Gln Phe Asp Tyr Gly
            500                 505                 510

Arg Lys Cys Ser Glu Val Ala Arg Leu Thr Glu Gly Met Ser Gly Arg
        515                 520                 525
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Glu Ile Ala Gln Leu Ala Val Ser Trp Gln Ala Thr Ala Tyr Ala Ser
530 535 540

Glu Asp Gly Val Leu Thr Glu Ala Met Met Asp Thr Arg Val Gln Asp
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Ala Val Gln Gln His Gln Gln Lys Met Cys Trp Leu Lys Ala Glu Gly
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Pro Gly Arg Gly Asp Glu Pro Ser Pro Ser
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<211> 2421

<212> DNA

<213> Mus musculus

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<212> PRT
<213> Mus musculus

<400> 16

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Asn Glu Asp Asn Ser Val Val Ser Leu Ser Gln Pro Lys Met Asp Glu
35 40 45

Leu Gln Leu Phe Arg Gly Asp Thr Val Leu Leu Lys Gly Lys Lys Arg
50 55 60

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Arg Glu Ala Val Cys Ile Val Leu Ser Asp Asp Thr Cys Ser Asp Glu
65                  70                  75                  80

Lys Ile Arg Met Asn Arg Val Val Arg Asn Asn Leu Arg Val Arg Leu
                85                  90                  95

Gly Asp Val Ile Ser Ile Gln Pro Cys Pro Asp Val Lys Tyr Gly Lys
            100                 105                 110

Arg Ile His Val Leu Pro Ile Asp Asp Thr Val Glu Gly Ile Thr Gly
        115                 120                 125

Asn Leu Phe Glu Val Tyr Leu Lys Pro Tyr Phe Leu Glu Ala Tyr Arg
    130                 135                 140

Pro Ile Arg Lys Gly Asp Ile Phe Leu Val Arg Gly Gly Met Arg Ala
145                 150                 155                 160

Val Glu Phe Lys Val Val Glu Thr Asp Pro Ser Pro Tyr Cys Ile Val
                165                 170                 175

Ala Pro Asp Thr Val Ile His Cys Glu Gly Glu Pro Ile Lys Arg Glu
            180                 185                 190

Asp Glu Glu Glu Ser Leu Asn Glu Val Gly Tyr Asp Asp Ile Gly Gly
        195                 200                 205

Cys Arg Lys Gln Leu Ala Gln Ile Lys Glu Met Val Glu Leu Pro Leu
    210                 215                 220

Arg His Pro Ala Leu Phe Lys Ala Ile Gly Val Lys Pro Pro Arg Gly
225                 230                 235                 240

Ile Leu Leu Tyr Gly Pro Pro Gly Thr Gly Lys Thr Leu Ile Ala Arg
                245                 250                 255

Ala Val Ala Asn Glu Thr Gly Ala Phe Phe Phe Leu Ile Asn Gly Pro
            260                 265                 270

Glu Ile Met Ser Lys Leu Ala Gly Glu Ser Glu Ser Asn Leu Arg Lys
        275                 280                 285

Ala Phe Glu Glu Ala Glu Lys Asn Ala Pro Ala Ile Ile Phe Ile Asp
    290                 295                 300

Glu Leu Asp Ala Ile Ala Pro Lys Arg Glu Lys Thr His Gly Glu Val
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Glu Arg Arg Ile Val Ser Gln Leu Leu Thr Leu Met Asp Gly Leu Lys
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Gln Arg Ala His Val Ile Val Met Ala Ala Thr Asn Arg Pro Asn Ser
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340 345 350

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355 360 365

Ile Gly Ile Pro Asp Ala Thr Gly Arg Leu Glu Ile Leu Gln Ile His
370 375 380

Thr Lys Asn Met Lys Leu Ala Asp Asp Val Asp Leu Glu Gln Val Ala
385 390 395 400

Asn Glu Thr His Gly His Val Gly Ala Asp Leu Ala Ala Leu Cys Ser
405 410 415

Glu Ala Ala Leu Gln Ala Ile Arg Lys Lys Met Asp Leu Ile Asp Leu
420 425 430

Glu Asp Glu Thr Ile Asp Ala Glu Val Met Asn Ser Leu Ala Val Thr
435 440 445

Met Asp Asp Phe Arg Trp Ala Leu Ser Gln Ser Asn Pro Ser Ala Leu
450 455 460

Arg Glu Thr Val Val Glu Val Pro Gln Val Thr Trp Glu Asp Ile Gly
465 470 475 480

Gly Leu Glu Asp Val Lys Arg Glu Leu Gln Glu Leu Val Gln Tyr Pro
485 490 495

Val Glu His Pro Asp Lys Phe Leu Lys Phe Gly Met Thr Pro Ser Lys
500 505 510

Gly Val Leu Phe Tyr Gly Pro Pro Gly Cys Gly Lys Thr Leu Leu Ala
515 520 525

Lys Ala Ile Ala Asn Glu Cys Gln Ala Asn Phe Ile Ser Ile Lys Gly
530 535 540

Pro Glu Leu Leu Thr Met Trp Phe Gly Glu Ser Glu Ala Asn Val Arg
545 550 555 560

Glu Ile Phe Asp Lys Ala Arg Gln Ala Ala Pro Cys Val Leu Phe Phe
565 570 575

Asp Glu Leu Asp Ser Ile Ala Lys Ala Arg Gly Gly Asn Ile Gly Asp
580 585 590

Gly Gly Gly Ala Ala Asp Arg Val Ile Asn Gln Ile Leu Thr Glu Met
595 600 605

Asp Gly Met Ser Thr Lys Lys Asn Val Phe Ile Ile Gly Ala Thr Asn
610 615 620

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Arg Pro Asp Ile Ile Asp Pro Ala Ile Leu Arg Pro Gly Arg Leu Asp
625                 630                 635                 640

Gln Leu Ile Tyr Ile Pro Leu Pro Asp Glu Lys Ser Arg Val Ala Ile
                645                 650                 655

Leu Lys Ala Asn Leu Arg Lys Ser Pro Val Ala Lys Asp Val Asp Leu
            660                 665                 670

Glu Phe Leu Ala Lys Met Thr Asn Gly Phe Ser Gly Ala Asp Leu Thr
        675                 680                 685

Glu Ile Cys Gln Arg Ala Cys Lys Leu Ala Ile Arg Glu Ser Ile Glu
    690                 695                 700

Ser Glu Ile Arg Arg Glu Arg Glu Arg Gln Thr Asn Pro Ser Ala Met
705                 710                 715                 720

Glu Val Glu Glu Asp Asp Pro Val Pro Glu Ile Arg Arg Asp His Phe
                725                 730                 735

Glu Glu Ala Met Arg Phe Ala Arg Arg Ser Val Ser Asp Asn Asp Ile
            740                 745                 750

Arg Lys Tyr Glu Met Phe Ala Gln Thr Leu Gln Gln Ser Arg Gly Phe
        755                 760                 765

Gly Ser Phe Arg Phe Pro Ser Gly Asn Gln Gly Gly Ala Gly Pro Ser
    770                 775                 780

Gln Gly Ser Gly Gly Gly Thr Gly Gly Ser Val Tyr Thr Glu Asp Asn
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Asp Asp Asp Leu Tyr Gly
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<210> 17

<211> 2870

<212> DNA

<213> Rattus norvegicus

<400> 17

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ggtttgtcac tgctgttgct cctccacctg agtgagtcaa gcccgggcct agtcggtcgc    180

ctaccattct cgtagccgtt accctcaggc cgccacagcc gccgaccggg agaggcgcgc    240
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<210> 18

<211> 806

<212> PRT

<213> Rattus norvegicus

<400> 18

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Asn Glu Asp Asn Ser Val Val Ser Leu Ser Gln Pro Lys Met Asp Glu
35 40 45

Leu Gln Leu Phe Arg Gly Asp Thr Val Leu Leu Lys Gly Lys Lys Arg
50 55 60

Arg Glu Ala Val Cys Ile Val Leu Ser Asp Asp Thr Cys Ser Asp Glu
65 70 75 80

Lys Ile Arg Met Asn Arg Val Val Arg Asn Asn Leu Arg Val Arg Leu
85 90 95

Gly Asp Val Ile Ser Ile Gln Pro Cys Pro Asp Val Lys Tyr Gly Lys
100 105 110

Arg Ile His Val Leu Pro Ile Asp Asp Thr Val Glu Gly Ile Thr Gly
115 120 125

Asn Leu Phe Glu Val Tyr Leu Lys Pro Tyr Phe Leu Glu Ala Tyr Arg
130 135 140

Pro Ile Arg Lys Gly Asp Ile Phe Leu Val Arg Gly Gly Met Arg Ala

145 150 155 160

Val Glu Phe Lys Val Val Glu Thr Asp Pro Ser Pro Tyr Cys Ile Val
165 170 175

Ala Pro Asp Thr Val Ile His Cys Glu Gly Glu Pro Ile Lys Arg Glu
180 185 190

Asp Glu Glu Glu Ser Leu Asn Glu Val Gly Tyr Asp Asp Ile Gly Gly
195 200 205

Cys Arg Lys Gln Leu Ala Gln Ile Lys Glu Met Val Glu Leu Pro Leu
210 215 220

Arg His Pro Ala Leu Phe Lys Ala Ile Gly Val Lys Pro Pro Arg Gly
225 230 235 240

Ile Leu Leu Tyr Gly Pro Pro Gly Thr Gly Lys Thr Leu Ile Ala Arg
245 250 255

Ala Val Ala Asn Glu Thr Gly Ala Phe Phe Phe Leu Ile Asn Gly Pro
260 265 270

Glu Ile Met Ser Lys Leu Ala Gly Glu Ser Glu Ser Asn Leu Arg Lys
275 280 285

Ala Phe Glu Glu Ala Glu Lys Asn Ala Pro Ala Ile Ile Phe Ile Asp
290 295 300

Glu Leu Asp Ala Ile Ala Pro Lys Arg Glu Lys Thr His Gly Glu Val
305 310 315 320

Glu Arg Arg Ile Val Ser Gln Leu Leu Thr Leu Met Asp Gly Leu Lys
325 330 335

Gln Arg Ala His Val Ile Val Met Ala Ala Thr Asn Arg Pro Asn Ser
340 345 350

Ile Asp Pro Ala Leu Arg Arg Phe Gly Arg Phe Asp Arg Glu Val Asp
355 360 365

Ile Gly Ile Pro Asp Ala Thr Gly Arg Leu Glu Ile Leu Gln Ile His
370 375 380

Thr Lys Asn Met Lys Leu Ala Asp Asp Val Asp Leu Glu Gln Val Ala
385 390 395 400

Asn Glu Thr His Gly His Val Gly Ala Asp Leu Ala Ala Leu Cys Ser
405 410 415

Glu Ala Ala Leu Gln Ala Ile Arg Lys Lys Met Asp Leu Ile Asp Leu
420 425 430

Glu Asp Glu Thr Ile Asp Ala Glu Val Met Asn Ser Leu Ala Val Thr
435 440 445

Met Asp Asp Phe Arg Trp Ala Leu Ser Gln Ser Asn Pro Ser Ala Leu
450 455 460

Arg Glu Thr Val Val Glu Val Pro Gln Val Thr Trp Glu Asp Ile Gly
465 470 475 480

Gly Leu Glu Asp Val Lys Arg Glu Leu Gln Glu Leu Val Gln Tyr Pro
485 490 495

Val Glu His Pro Asp Lys Phe Leu Lys Phe Gly Met Thr Pro Ser Lys
500 505 510

Gly Val Leu Phe Tyr Gly Pro Pro Gly Cys Gly Lys Thr Leu Leu Ala
515 520 525

Lys Ala Ile Ala Asn Glu Cys Gln Ala Asn Phe Ile Ser Ile Lys Gly
530 535 540

Pro Glu Leu Leu Thr Met Trp Phe Gly Glu Ser Glu Ala Asn Val Arg
545 550 555 560

Glu Ile Phe Asp Lys Ala Arg Gln Ala Ala Pro Cys Val Leu Phe Phe
565 570 575

Asp Glu Leu Asp Ser Ile Ala Lys Ala Arg Gly Gly Asn Ile Gly Asp
580 585 590

Gly Gly Gly Ala Ala Asp Arg Val Ile Asn Gln Ile Leu Thr Glu Met
595 600 605

Asp Gly Met Ser Thr Lys Lys Asn Val Phe Ile Ile Gly Ala Thr Asn
610 615 620

Arg Pro Asp Ile Ile Asp Pro Ala Ile Leu Arg Pro Gly Arg Leu Asp
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Gln Leu Ile Tyr Ile Pro Leu Pro Asp Glu Lys Ser Arg Val Ala Ile
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Leu Lys Ala Asn Leu Arg Lys Ser Pro Val Ala Lys Asp Val Asp Leu
660 665 670

Glu Phe Leu Ala Lys Met Thr Asn Gly Phe Ser Gly Ala Asp Leu Thr
675 680 685

Glu Ile Cys Gln Arg Ala Cys Lys Leu Ala Ile Arg Glu Ser Ile Glu
690 695 700

Ser Glu Ile Arg Arg Glu Arg Glu Arg Gln Thr Asn Pro Ser Ala Met
705 710 715 720

Glu Val Glu Glu Asp Asp Pro Val Pro Glu Ile Arg Arg Asp His Phe
725 730 735

Glu Glu Ala Met Arg Phe Ala Arg Arg Ser Val Ser Asp Asn Asp Ile
740 745 750

Arg Lys Tyr Glu Met Phe Ala Gln Thr Leu Gln Gln Ser Arg Gly Phe
755 760 765

Gly Ser Phe Arg Phe Pro Ser Gly Asn Gln Gly Gly Ala Gly Pro Ser
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Gln Gly Ser Gly Gly Gly Thr Gly Gly Asn Val Tyr Thr Glu Asp Asn
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Asp Asp Asp Leu Tyr Gly
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<211> 2751

<212> DNA

<213> Drosophila melanogaster

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aactgtgccc cgccccccgt caaggccaac aagtgggcca tcagcaacaa caactacctg 180

gagtcgctcg aggagcagca gcagcaacag caatcgccat cggagccagc tgttgagtcc 240

aacaacaacc acattgtttt agaagcatca atggatgcgt tgaagccaac ggagccaagt 300

attagcaatg gtcatgaagt tactaccgcc gtcgcagcaa tgaaaagtca agcggaggtg 360

ccactcccgc caacagcgag tgcggcgata ccggaggaca gtatcgccag gttagaggtg 420

gtcacctcag ccgttccttg tgagccctgg acgagcaatg ggcccactac tccttccgcg 480

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gagagcatca tacccaccta ctgtcccatg cgctatcatc cctttgtacc gcatccgcac 720

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<210> 20
<211> 599
<212> PRT

<213> Drosophila melanogaster

<400> 20

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Thr Ala Gly Glu Lys Ser Gly Asp Ser Gln Leu Ser Arg Ala Glu Arg
        35                  40                  45

Lys Ala Met Glu Ala Tyr Arg Phe Asp Ser Ser Ala Leu Glu Arg Ala
    50                  55                  60

Ala Asp Ala Ala Lys Thr Leu Glu Arg Ser Lys His Ala Arg Glu Ala
65                  70                  75                  80

Leu Glu Leu Ser Lys Met Gln Glu Ala Thr Arg Gln Thr Glu Tyr Asn
                85                  90                  95

Thr Lys Val Lys Glu Tyr Glu Ala His Ile Glu Gln Ala Lys Val Glu
            100                 105                 110

Gln Lys Arg Ile Asp His Glu Glu Arg Arg Lys Thr Leu Ile Glu Glu
        115                 120                 125

Thr Lys Gln Gln Gln Gln Arg Ala Gln Tyr Gln Asp Gln Leu Ser Arg
    130                 135                 140

Lys Arg Tyr Glu Asp Gln Leu Leu Gln Gln Gln Arg Val Gln Glu Glu
145                 150                 155                 160

Asn Leu Arg Lys Gln Glu Glu Ser Val Gln Arg Gln Glu Ala Met Arg
                165                 170                 175

Arg Gln Thr Ile Glu His Glu Ile Glu Met Lys Glu Lys Asn Arg Leu
            180                 185                 190

Lys Leu Leu Glu His Glu Leu Arg Ala Lys Ala Arg Val Asp Arg Glu
        195                 200                 205

Asn Arg Asp Ile Asn Leu Glu Lys Ile Arg Leu Lys Ala Gln Glu His
    210                 215                 220

Arg Thr Thr Val Leu Glu Gly Ile Lys Thr Ala Gly Thr Val Ile Gly
225                 230                 235                 240

Ala Gly Ala Glu Ala Met Leu Thr Asp Trp Asp Lys Val Leu Thr Ala
                245                 250                 255
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Ala Gly Gly Leu Ser Leu Leu Ala Leu Gly Val Tyr Thr Ala Lys Gly
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Ala Thr Gly Val Val Ser Arg Tyr Val Glu Ala Arg Ile Gly Lys Pro
275 280 285

Thr Leu Val Gly Glu Thr Ser Arg Phe Ala Phe Leu Asp Ala Leu Lys
290 295 300

Asn Pro Leu His Tyr Leu Lys Arg Leu Arg Ala Lys Pro Thr Asp Ala
305 310 315 320

Leu Gln Gly Val Val Leu Asn Pro Lys Leu Glu Glu Arg Leu Arg Asp
325 330 335

Ile Ala Ile Ala Thr Lys Asn Thr Arg Ile Asn Lys Gly Met Tyr Arg
340 345 350

Asn Val Leu Met His Gly Pro Pro Gly Thr Gly Lys Thr Met Phe Ala
355 360 365

Lys Lys Leu Ala Glu His Ser Gly Met Asp Phe Ala Ile Met Thr Gly
370 375 380

Gly Asp Val Ala Pro Met Gly Lys Glu Gly Val Thr Ala Ile His Lys
385 390 395 400

Val Phe Asp Trp Ser His Thr Ser Arg Arg Gly Leu Leu Leu Phe Val
405 410 415

Asp Glu Ala Asp Ala Phe Leu Arg Lys Arg Ser Ser Glu Lys Ile Ser
420 425 430

Glu Asp Leu Arg Ala Ala Leu Asn Ala Phe Leu Tyr Arg Thr Ser Glu
435 440 445

Gln Asn Pro Lys Phe Met Leu Val Leu Ala Ser Asn Thr Pro Glu Gln
450 455 460

Phe Asp Tyr Ala Ile Asn Asp Arg Leu Asp Glu Met Val Glu Phe Thr
465 470 475 480

Leu Pro Gly Leu Glu Glu Arg Glu Arg Leu Leu Arg Leu Tyr Phe Asp
485 490 495

Lys Tyr Val Leu Gln Pro Ala Ala Ala Gly Ala Lys Arg Phe Lys Leu
500 505 510

Asp Thr Phe Asp Tyr Gly Lys Thr Cys Ser Lys Met Ala Ala Leu Cys
515 520 525

Glu Gly Met Ser Gly Arg Glu Ile Ser Lys Leu Gly Val Ser Trp Gln
530 535 540

Ala Ala Val Tyr Ala Ser Glu Asp Gly Leu Leu Thr Glu Lys Met Val
545 550 555 560

Leu Asp Arg Cys Tyr Ser Ala Ala Gln Gln His Lys Gln Lys Arg Trp
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Pro Gly Phe Arg Ile Arg Ser Val Leu Ile Thr Asn Pro Ser Gln Ala
580 585 590

Gln Leu Pro His Pro Ser Pro
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<211> 2244

<212> DNA

<213> Saccharomyces cerevisiae

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attcctacaa tgttaaatgc atga 2244

<210> 22
<211> 747
<212> PRT
<213> Saccharomyces cerevisiae

<400> 22

Met Asn Val Ser Lys Ile Leu Val Ser Pro Thr Val Thr Thr Asn Val
1 5 10 15

Leu Arg Ile Phe Ala Pro Arg Leu Pro Gln Ile Gly Ala Ser Leu Leu
20 25 30

Val Gln Lys Lys Trp Ala Leu Arg Ser Lys Lys Phe Tyr Arg Phe Tyr
35 40 45

Ser Glu Lys Asn Ser Gly Glu Met Pro Pro Lys Lys Glu Ala Asp Ser
50 55 60

Ser Gly Lys Ala Ser Asn Lys Ser Thr Ile Ser Ser Ile Asp Asn Ser

65 70 75 80

Gln Pro Pro Pro Pro Ser Asn Thr Asn Asp Lys Thr Lys Gln Ala Asn
85 90 95

Val Ala Val Ser His Ala Met Leu Ala Thr Arg Glu Gln Glu Ala Asn
100 105 110

Lys Asp Leu Thr Ser Pro Asp Ala Gln Ala Ala Phe Tyr Lys Leu Leu
115 120 125

Leu Gln Ser Asn Tyr Pro Gln Tyr Val Val Ser Arg Phe Glu Thr Pro
130 135 140

Gly Ile Ala Ser Ser Pro Glu Cys Met Glu Leu Tyr Met Glu Ala Leu
145 150 155 160

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

Leu Thr Ala Ser Ser Ala Gly Ala Val Asn Pro Ser Leu Ala Ser Ser
180 185 190

Ser Ser Asn Gln Ser Gly Tyr His Gly Asn Phe Pro Ser Met Tyr Ser
195 200 205

Pro Leu Tyr Gly Ser Arg Lys Glu Pro Leu His Val Val Val Ser Glu
210 215 220

Ser Thr Phe Thr Val Val Ser Arg Trp Val Lys Trp Leu Leu Val Phe
225 230 235 240

Gly Ile Leu Thr Tyr Ser Phe Ser Glu Gly Phe Lys Tyr Ile Thr Glu
245 250 255

Asn Thr Thr Leu Leu Lys Ser Ser Glu Val Ala Asp Lys Ser Val Asp
260 265 270

Val Ala Lys Thr Asn Val Lys Phe Asp Asp Val Cys Gly Cys Asp Glu
275 280 285

Ala Arg Ala Glu Leu Glu Glu Ile Val Asp Phe Leu Lys Asp Pro Thr
290 295 300

Lys Tyr Glu Ser Leu Gly Gly Lys Leu Pro Lys Gly Val Leu Leu Thr
305 310 315 320

Gly Pro Pro Gly Thr Gly Lys Thr Leu Leu Ala Arg Ala Thr Ala Gly
325 330 335

Glu Ala Gly Val Asp Phe Phe Phe Met Ser Gly Ser Glu Phe Asp Glu
340 345 350

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

Ala Arg Ser Arg Ala Pro Ala Ile Ile Phe Ile Asp Glu Leu Asp Ala
370 375 380

Ile Gly Gly Lys Arg Asn Pro Lys Asp Gln Ala Tyr Ala Lys Gln Thr
385 390 395 400

Leu Asn Gln Leu Leu Val Glu Leu Asp Gly Phe Ser Gln Thr Ser Gly
405 410 415

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

Leu Thr Arg Pro Gly Arg Phe Asp Lys Val Val Asn Val Asp Leu Pro
435 440 445

Asp Val Arg Gly Arg Ala Asp Ile Leu Lys His His Met Lys Lys Ile
450 455 460

Thr Leu Ala Asp Asn Val Asp Pro Thr Ile Ile Ala Arg Gly Thr Pro
465 470 475 480

Gly Leu Ser Gly Ala Glu Leu Ala Asn Leu Val Asn Gln Ala Ala Val
485 490 495

Tyr Ala Cys Gln Lys Asn Ala Val Ser Val Asp Met Ser His Phe Glu
500 505 510

Trp Ala Lys Asp Lys Ile Leu Met Gly Ala Glu Arg Lys Thr Met Val
515 520 525

Leu Thr Asp Ala Ala Arg Lys Ala Thr Ala Phe His Glu Ala Gly His
530 535 540

Ala Ile Met Ala Lys Tyr Thr Asn Gly Ala Thr Pro Leu Tyr Lys Ala
545 550 555 560

Thr Ile Leu Pro Arg Gly Arg Ala Leu Gly Ile Thr Phe Gln Leu Pro
565 570 575

Glu Met Asp Lys Val Asp Ile Thr Lys Arg Glu Cys Gln Ala Arg Leu
580 585 590

Asp Val Cys Met Gly Gly Lys Ile Ala Glu Glu Leu Ile Tyr Gly Lys
595 600 605

Asp Asn Thr Thr Ser Gly Cys Gly Ser Asp Leu Gln Ser Ala Thr Gly
610 615 620

Thr Ala Arg Ala Met Val Thr Gln Tyr Gly Met Ser Asp Asp Val Gly
625 630 635 640

Pro Val Asn Leu Ser Glu Asn Trp Glu Ser Trp Ser Asn Lys Ile Arg
645 650 655

Asp Ile Ala Asp Asn Glu Val Ile Glu Leu Leu Lys Asp Ser Glu Glu
660 665 670

Arg Ala Arg Arg Leu Leu Thr Lys Lys Asn Val Glu Leu His Arg Leu
675 680 685

Ala Gln Gly Leu Ile Glu Tyr Glu Thr Leu Asp Ala His Glu Ile Glu
690 695 700

Gln Val Cys Lys Gly Glu Lys Leu Asp Lys Leu Lys Thr Ser Thr Asn
705 710 715 720

Thr Val Val Glu Gly Pro Asp Ser Asp Glu Arg Lys Asp Ile Gly Asp
725 730 735

Asp Lys Pro Lys Ile Pro Thr Met Leu Asn Ala
740 745

<210> 23

<211> 189

<212> DNA

<213> Caenorhabditis elegans

<400> 23
atggataaat ctgacatgca acgaaccgtc gactcgcttc gcagccagct caatattgag 60

cgtactccga tcactgtttc ggcagccgaa cttcgtcgct tcaccgaaag ccaagaagat 120

ccacttgtga acccaatcga caagaaggtt aacccatggg ctgagaagag caagtgcagc 180

atgctctaa 189

<210> 24

<211> 62

<212> PRT

<213> Caenorhabditis elegans

<400> 24

Met Asp Lys Ser Asp Met Gln Arg Thr Val Asp Ser Leu Arg Ser Gln
1 5 10 15

Leu Asn Ile Glu Arg Thr Pro Ile Thr Val Ser Ala Ala Glu Leu Arg
20 25 30

Arg Phe Thr Glu Ser Gln Glu Asp Pro Leu Val Asn Pro Ile Asp Lys
35 40 45

Lys Val Asn Pro Trp Ala Glu Lys Ser Lys Cys Ser Met Leu
50 55 60

<210> 25

<211> 204

<212> DNA

<213> Homo sapiens

<400> 25
atggaggagt gggacgtgcc acagatgaag aaagaggtgg agagccttaa gtaccagctg 60

gccttccagc gggagatggc gtccaagacc atccccgagc tgctgaagtg gatcgaggac 120

gggatcccca aggacccctt cctgaacccc gacctgatga agaacaaccc atgggtggaa 180

aagggcaaat gcaccatcct gtga 204

<210> 26

<211> 67

<212> PRT

<213> Homo sapiens

<400> 26

Met Glu Glu Trp Asp Val Pro Gln Met Lys Lys Glu Val Glu Ser Leu
1 5 10 15

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

Glu Leu Leu Lys Trp Ile Glu Asp Gly Ile Pro Lys Asp Pro Phe Leu
35 40 45

Asn Pro Asp Leu Met Lys Asn Asn Pro Trp Val Glu Lys Gly Lys Cys
50 55 60

Thr Ile Leu
65

<210> 27

<211> 560

<212> DNA

<213> Rattus norvegicus

<400> 27
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gaggaggcgg tcctgagggg ctgcacccca ggggaggggg cggggctggg aatgggatct 180
gcagaaccgc cagccatccc agccctgagc tgcaacagcc atgtccaaca acatggccaa 240
gatcgctgag gcccgcaaga cggtggagca actgaagctg gaggtgaaca tcgatcgcat 300
gaaggtgtcg caggcggcag cggagctatt ggctttctgc gaaacgcacg ctaaggatga 360
cccactggtg actcctgtcc ctgccgccga gaatcccttc cgcgacaaac gactcttttg 420
caccctgctc tgagccccca agatagtttt atcctcccgc gcagaaatat gaatccaata 480
aacttggtga cttggtggtg cctgccattt aggggaaaat gaggcacggg gcaaaaacgt 540
gggggccacc tttgtgggga 560

<210> 28
<211> 70
<212> PRT
<213> Rattus norvegicus

<400> 28
Met Ser Asn Asn Met Ala Lys Ile Ala Glu Ala Arg Lys Thr Val Glu
1 5 10 15

Gln Leu Lys Leu Glu Val Asn Ile Asp Arg Met Lys Val Ser Gln Ala
20 25 30

Ala Ala Glu Leu Leu Ala Phe Cys Glu Thr His Ala Lys Asp Asp Pro
35 40 45

Leu Val Thr Pro Val Pro Ala Ala Glu Asn Pro Phe Arg Asp Lys Arg
50 55 60

Leu Phe Cys Thr Leu Leu
65 70

<210> 29
<211> 558
<212> DNA
<213> Drosophila melanogaster

<400> 29
atggatccca gtgctctaca aaacatggat cgggacgcat taaagaagca aatcgagaat 60
atgaaatatc aggcctccat ggagcgctgg ccgttatcta atccatagc agaaatgcgc 120
tcgttcatcg aggagaacga gaaaaatgat ccgttgatca atgcgccgga taagaagaac 180
aatccatggg ccgaaaaggg caaatgccct caacatcatc agcaattaga tacccctagc 240
caatgtagca gccaagtttt ggggcaggat ttgggtgaat ccccggatct ggtgccggta 300
gagatgcagc actacaacaa caactactac tactattaca actacaactt gagctatgag 360
ccgccggtcg atcggtcgct gggcggcggg ggcaagcgga gcattcaacg tctgcagcaa 420
ctggtgcgaa ggacgcggta cgagctgcag caatggccgc tactgatgca gctgctcctg 480
ttcgtccttt ggctaaatgc caagttctgg cagctggtca acgaacaggt gacctaccgc 540
cgcaggaggt ggcactga 558

<210> 30
<211> 185
<212> PRT
<213> Drosophila melanogaster

<400> 30
Met Asp Pro Ser Ala Leu Gln Asn Met Asp Arg Asp Ala Leu Lys Lys
1 5 10 15

Gln Ile Glu Asn Met Lys Tyr Gln Ala Ser Met Glu Arg Trp Pro Leu
20 25 30

Ser Lys Ser Ile Ala Glu Met Arg Ser Phe Ile Glu Glu Asn Glu Lys
35 40 45

Asn Asp Pro Leu Ile Asn Ala Pro Asp Lys Lys Asn Asn Pro Trp Ala
50 55 60

Glu Lys Gly Lys Cys Pro Gln His His Gln Gln Leu Asp Thr Pro Ser
65 70 75 80

Gln Cys Ser Ser Gln Val Leu Gly Gln Asp Leu Gly Glu Ser Pro Asp
85 90 95

Leu Val Pro Val Glu Met Gln His Tyr Asn Asn Asn Tyr Tyr Tyr Tyr
100 105 110

Tyr Asn Tyr Asn Leu Ser Tyr Glu Pro Pro Val Asp Arg Ser Leu Gly
115 120 125

Gly Gly Gly Lys Arg Ser Ile Gln Arg Leu Gln Gln Leu Val Arg Arg
130 135 140

Thr Arg Tyr Glu Leu Gln Gln Trp Pro Leu Leu Met Gln Leu Leu Leu
145 150 155 160

Phe Val Leu Trp Leu Asn Ala Lys Phe Trp Gln Leu Val Asn Glu Gln
165 170 175

Val Thr Tyr Arg Arg Arg Arg Trp His
180 185

<210> 31

<211> 705

<212> DNA

<213> Caenorhabditis elegans

<400> 31
atgtttagtc aaaacccgta cgagtcacac gtcgacgtcg ccgtatctgc agcttcagct 60

aatctccgga atatgacaaa cgaacaatta atttcgttgc tagacgatga tgcccttta 120

gaatcgatta ttgtcaatct cccgcaggtc cgctcaatgc cgactgataa ggaatcagct 180

cttgccgcaa ataaatcatt agcagaatgg aatttagctc aaaagccgag aatcgatgct 240

gccaaaacgc aaacggttga tctctacgac caagtaaaaa agctccaagg agaagttgcc 300

gtgctgaaaa gtcaattgga ctctgtttcc tcatcaaaat cacttgatac aacatcgagc 360

ttgatgcaag tcgccgcaca agaagctgat gatgatgcag aagccctatt cacacaattt 420

gaaaatggag aaatatccgt ggaaattttc ctgaagcaat tcaaagataa gaagacaatt 480

gctcatctac gaaaaatcaa gtctgaccgt ctcgcagcac ttcttcgtga acaaacgtat 540

tcttcatatg ctcaaccaac tgtacctcct ccaatgccac acgctcagcc tggataccca 600

acaggaaatc acatgcctgg aataggaaat attcaattcg gatctggcta ttcaggatat 660

ccaaatattt ctcaaccttc tgctggtcgt catccatttt tctga 705

<210> 32

<211> 234

<212> PRT

<213> Caenorhabditis elegans

<400> 32

Met Phe Ser Gln Asn Pro Tyr Glu Ser His Val Asp Val Ala Val Ser
1 5 10 15

Ala Ala Ser Ala Asn Leu Arg Asn Met Thr Asn Glu Gln Leu Ile Ser
20 25 30

Leu Leu Asp Asp Asp Ala Leu Leu Glu Ser Ile Ile Val Asn Leu Pro
35 40 45

Gln Val Arg Ser Met Pro Thr Asp Lys Glu Ser Ala Leu Ala Ala Asn
50 55 60

Lys Ser Leu Ala Glu Trp Asn Leu Ala Gln Lys Pro Arg Ile Asp Ala
65 70 75 80

Ala Lys Thr Gln Thr Val Asp Leu Tyr Asp Gln Val Lys Lys Leu Gln
85 90 95

Gly Glu Val Ala Val Leu Lys Ser Gln Leu Asp Ser Val Ser Ser Ser
100 105 110

Lys Ser Leu Asp Thr Thr Ser Ser Leu Met Gln Val Ala Ala Gln Glu
115 120 125

Ala Asp Asp Asp Ala Glu Ala Leu Phe Thr Gln Phe Glu Asn Gly Glu
130 135 140

Ile Ser Val Glu Ile Phe Leu Lys Gln Phe Lys Asp Lys Lys Thr Ile
145 150 155 160

Ala His Leu Arg Lys Ile Lys Ser Asp Arg Leu Ala Ala Leu Leu Arg
165 170 175

Glu Gln Thr Tyr Ser Ser Tyr Ala Gln Pro Thr Val Pro Pro Pro Met
180 185 190

Pro His Ala Gln Pro Gly Tyr Pro Thr Gly Asn His Met Pro Gly Ile
195 200 205

Gly Asn Ile Gln Phe Gly Ser Gly Tyr Ser Gly Tyr Pro Asn Ile Ser
210 215 220

Gln Pro Ser Ala Gly Arg His Pro Phe Phe
225 230

<210> 33

<211> 858

<212> DNA

<213> Homo sapiens

<400> 33
atggcgggcg ccgggagcga agcccggttc gccgggctgt cgctggtgca gctcaacgag 60

ctgctggagg acgagggcca gctgacggag atggtgcaga agatggagga gacacagaat 120

gttcagctta acaaagaaat gacacttgcc agcaaccgga gcctggcaga aggaaacctt 180

ttgtaccagc cccagctgga cacgttgaaa gcacgcttga cccagaaata ccaggaactc 240

caggttctct ttgaagccta tcagataaag aagaccaaat tagacagaca gtctagcagt 300

gcttccttgg agaccctgtt agcacttctt caggcagaag gggccaagat tgaggaagac 360

actgagaaca tggcagagaa gtttctggat ggagaacttc ctctggattc cttcattgat 420

gtctatcaga gcaaacggaa actggcccac atgcgacggg tgaaaatcga gaagctccag 480

gagatggtcc taaaggggca gagactccca caggccctgg ccccgctgcc ccccaggctg 540

cccgaactgg cacctaccgc ccccttcccc taccctgccc cagaggccag tgggcctcct 600

gccgttgcac ctcggcgcat ccccccccca ccacccccgg tgcctgcggg acgcttagcc 660

accccgttta ctgcggccat gagttcggga caggccgtgc cgtacccagg attacagtgc 720

ccgcccctgc cccccgcgt gggcctcccc actcagcaag gattctcttc gcagttcgtg 780

tccccatatc cgccacctct ccctcagaga cccccgcccc ggctccctcc acaccagccg 840

ggtttcatcc tccagtga 858

<210> 34

<211> 285

<212> PRT

<213> Homo sapiens

<400> 34

Met Ala Gly Ala Gly Ser Glu Ala Arg Phe Ala Gly Leu Ser Leu Val
1 5 10 15

Gln Leu Asn Glu Leu Leu Glu Asp Glu Gly Gln Leu Thr Glu Met Val
20 25 30

Gln Lys Met Glu Glu Thr Gln Asn Val Gln Leu Asn Lys Glu Met Thr
35 40 45

Leu Ala Ser Asn Arg Ser Leu Ala Glu Gly Asn Leu Leu Tyr Gln Pro
50 55 60

Gln Leu Asp Thr Leu Lys Ala Arg Leu Thr Gln Lys Tyr Gln Glu Leu
65 70 75 80

Gln Val Leu Phe Glu Ala Tyr Gln Ile Lys Lys Thr Lys Leu Asp Arg
85 90 95

Gln Ser Ser Ser Ala Ser Leu Glu Thr Leu Leu Ala Leu Leu Gln Ala
100 105 110

Glu Gly Ala Lys Ile Glu Glu Asp Thr Glu Asn Met Ala Glu Lys Phe
115 120 125

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Leu Asp Gly Glu Leu Pro Leu Asp Ser Phe Ile Asp Val Tyr Gln Ser
    130                 135                 140

Lys Arg Lys Leu Ala His Met Arg Arg Val Lys Ile Glu Lys Leu Gln
145                 150                 155                 160

Glu Met Val Leu Lys Gly Gln Arg Leu Pro Gln Ala Leu Ala Pro Leu
                165                 170                 175

Pro Pro Arg Leu Pro Glu Leu Ala Pro Thr Ala Pro Leu Pro Tyr Pro
            180                 185                 190

Ala Pro Glu Ala Ser Gly Pro Pro Ala Val Ala Pro Arg Arg Ile Pro
        195                 200                 205

Pro Pro Pro Pro Pro Val Pro Ala Gly Arg Leu Ala Thr Pro Phe Thr
    210                 215                 220

Ala Ala Met Ser Ser Gly Gln Ala Val Pro Tyr Pro Gly Leu Gln Cys
225                 230                 235                 240

Pro Pro Leu Pro Pro Arg Val Gly Leu Pro Thr Gln Gln Gly Phe Ser
                245                 250                 255

Ser Gln Phe Val Ser Pro Tyr Pro Pro Pro Leu Pro Gln Arg Pro Pro
            260                 265                 270

Pro Arg Leu Pro Pro His Gln Pro Gly Phe Ile Leu Gln
        275                 280                 285
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<210> 35

<211> 1136

<212> DNA

<213> Homo sapiens

<400> 35

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actcggaggc gattgaccag ctggccctgg agtcccctga ggtccaggac ctacagctgg    180

aacgggagat ggcactggcc accaaccgga gcctggcaga gcggaacttg gagttccagg    240

gtcccctgga gatcagccgc tcaaacctct cggatagata ccaggagctc cggaagctcg    300

tggagcggtg ccaggagcag aaggcaaagc tggagaaatt ttcttcagca ctgcagccag    360

ggaccttgtt agaccttctg caggtggaag gcatgaagat cgaagaagag tccgaggcca    420

tggctgagaa gttcctggag ggcgaggtgc ccctggaaac gttcctggag aatttttcct    480

ccatgaggat gctgtcccac ctgcgccggg ttcgcgtgga aaagctccag gaagtggtga    540
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ggaagcccag ggcttcccag gagctggccg gcgatgcccc tccaccccgt ccaccacccc 600
cggtgcgccc agacccccag ggaacacccc ctgtggttga agagcagccg cagccaccat 660
tagccatgcc tccctaccct ttgccctaca gcccatcccc cagcctgcct gtgggcccca 720
ctgcccatgg agccctgcca ccggcccctt tcccagtagt gtcccagccc tccttctaca 780
gcgggcctct gggccccact tacccggcag cccagcttgg acccaggggt gctgcgggtt 840
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gtgcctctgg gcctgggtac cccttgcggg gaggcagggc ccccagtcct ggttatcctc 960
aacagtcccc ataccccgca acaggaggaa aacctcccta cccaatacag cctcagctcc 1020
ccagctttcc aggccagccc cagccctcag tgcccctgca gccccccttat ccccccgggc 1080
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<210> 36

<211> 377

<212> PRT

<213> Homo sapiens

<400> 36

Asp Ala Trp Ala Arg Leu Arg Phe Asn Pro Arg Trp Arg Arg Arg Arg
1 5 10 15

Arg Pro Trp Gln Gly Arg Met Glu Thr Leu Lys Asp Lys Thr Leu Gln
20 25 30

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

Leu Glu Ser Pro Glu Val Gln Asp Leu Gln Leu Glu Arg Glu Met Ala
50 55 60

Leu Ala Thr Asn Arg Ser Leu Ala Glu Arg Asn Leu Glu Phe Gln Gly
65 70 75 80

Pro Leu Glu Ile Ser Arg Ser Asn Leu Ser Asp Arg Tyr Gln Glu Leu
85 90 95

Arg Lys Leu Val Glu Arg Cys Gln Glu Gln Lys Ala Lys Leu Glu Lys
100 105 110

Phe Ser Ser Ala Leu Gln Pro Gly Thr Leu Leu Asp Leu Leu Gln Val
115 120 125

Glu Gly Met Lys Ile Glu Glu Glu Ser Glu Ala Met Ala Glu Lys Phe
130 135 140

Leu Glu Gly Glu Val Pro Leu Glu Thr Phe Leu Glu Asn Phe Ser Ser
145 150 155 160

Met Arg Met Leu Ser His Leu Arg Arg Val Arg Val Glu Lys Leu Gln
165 170 175

Glu Val Val Arg Lys Pro Arg Ala Ser Gln Glu Leu Ala Gly Asp Ala
180 185 190

Pro Pro Pro Arg Pro Pro Pro Pro Val Arg Pro Asp Pro Gln Gly Thr
195 200 205

Pro Pro Val Val Glu Glu Gln Pro Gln Pro Pro Leu Ala Met Pro Pro
210 215 220

Tyr Pro Leu Pro Tyr Ser Pro Ser Pro Ser Leu Pro Val Gly Pro Thr
225 230 235 240

Ala His Gly Ala Leu Pro Pro Ala Pro Phe Pro Val Val Ser Gln Pro
245 250 255

Ser Phe Tyr Ser Gly Pro Leu Gly Pro Thr Tyr Pro Ala Ala Gln Leu
260 265 270

Gly Pro Arg Gly Ala Ala Gly Tyr Ser Trp Ser Pro Gln Arg Ser Met
275 280 285

Pro Pro Arg Pro Gly Tyr Pro Gly Thr Pro Met Gly Ala Ser Gly Pro
290 295 300

Gly Tyr Pro Leu Arg Gly Gly Arg Ala Pro Ser Pro Gly Tyr Pro Gln
305 310 315 320

Gln Ser Pro Tyr Pro Ala Thr Gly Gly Lys Pro Pro Tyr Pro Ile Gln
325 330 335

Pro Gln Leu Pro Ser Phe Pro Gly Gln Pro Gln Pro Ser Val Pro Leu
340 345 350

Gln Pro Pro Tyr Pro Pro Gly Pro Ala Pro Pro Tyr Gly Phe Pro Pro
355 360 365

Pro Pro Gly Pro Ala Trp Pro Gly Tyr
370 375

<210> 37

<211> 645

<212> DNA

<213> Drosophila melanogaster

<400> 37
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ctgaaggaac tgctgaacga tgacgacaag ctggacgaga aggttgacga agttctccag 120
gtgctccgaa cacaaaagac cagtgttttc gaggacaaca ggagtcgggc ggagcgcaat 180
atcgagcggg agccgcagat catcgagctg cgggggcagc tggcagaact ctcggaggat 240
gggcgcacca ggtgctcctc tgtccaggag aaactctcac agctcaagga gaagtcgggc 300
ggagtgggcc ttgaaacggc gctggccctg ctgcagacag ctgcctccga gagcgaggag 360
cagaccgagg agatggtcaa gaagttcaac gacagcgata tcggcgtgga ggactttctg 420
gacgcgttcc tccctatccg gaggaccatg cacctgcgtc gcctcaaggc cgaaaaaatg 480
caggagctga tgcgcaaaca gcgccagggt ccgggcccaa atacttctct gccagcctac 540
ggaaacgtgc cctccagcgg attctatccc gcgtctgggg gctccgcccc ttacccaatc 600
atgggtcccc tgatgcccat gccaccgcca tccagaccgt actga 645

<210> 38
<211> 214
<212> PRT
<213> Drosophila melanogaster

<400> 38
Met Tyr Gln Glu Tyr Leu Tyr Gln Leu Arg Ala Thr Ile Thr Pro Met
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Cys His Glu Glu Leu Lys Glu Leu Leu Asn Asp Asp Asp Lys Leu Asp
20 25 30

Glu Lys Val Asp Glu Val Leu Gln Val Leu Arg Thr Gln Lys Thr Ser
35 40 45

Val Phe Glu Asp Asn Arg Ser Arg Ala Glu Arg Asn Ile Glu Arg Glu
50 55 60

Pro Gln Ile Ile Glu Leu Arg Gly Gln Leu Ala Glu Leu Ser Glu Asp
65 70 75 80

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

Glu Lys Ser Gly Gly Val Gly Leu Glu Thr Ala Leu Ala Leu Leu Gln
100 105 110

Thr Ala Ala Ser Glu Ser Glu Glu Gln Thr Glu Glu Met Val Lys Lys
115 120 125

Phe Asn Asp Ser Asp Ile Gly Val Glu Asp Phe Leu Asp Ala Phe Leu
130 135 140

Pro Ile Arg Arg Thr Met His Leu Arg Arg Leu Lys Ala Glu Lys Met
145 150 155 160

Gln Glu Leu Met Arg Lys Gln Arg Gln Gly Pro Gly Pro Asn Thr Ser
165 170 175

Leu Pro Ala Tyr Gly Asn Val Pro Ser Ser Gly Phe Tyr Pro Ala Ser
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Gly Gly Ser Ala Pro Tyr Pro Ile Met Gly Pro Leu Met Pro Met Pro
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Pro Pro Ser Arg Pro Tyr
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<211> 2319

<212> DNA

<213> Caenorhabditis elegans

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<213> Caenorhabditis elegans

<400> 40

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Pro Phe Lys Glu Glu Arg Ser Leu Glu Asp Leu Gln Ala Asp Leu Ala
35 40 45

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Asp Met Ala Val Trp Met Glu Gly Leu Asp Ala Thr Lys Leu Pro Leu
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Asn Asp Pro Gln Leu Leu Cys Asn Gly Arg Ala Phe Ser Glu Val Leu
65                  70                  75                  80

His Asn Val Asp Lys Asn Phe Phe Thr Asp Gly Trp Leu Glu Thr Met
                85                  90                  95

Pro Glu Asn Arg Thr Thr Asn Ile Met Val Phe Arg Ser Cys Thr Arg
            100                 105                 110

Lys Leu Trp Arg Lys Met Phe Asp Tyr Val Asn His Ile Asn Arg Thr
        115                 120                 125

Val Val Ser Ser Arg Trp Thr Asp Ile His Glu Arg Ile Asp Gly Ile
    130                 135                 140

Tyr Glu Ser Asp Leu Pro Ala Met Val Asn Leu Gly Met Ala Val Val
145                 150                 155                 160

Thr Leu Ala His Ile Gly Lys Asn Ala Lys Arg Phe Val Asp Tyr Ser
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Lys Ala Leu Thr Ser Thr His Lys Ser Met Met Ser Asn Val Ala Lys
            180                 185                 190

Met Val Thr Thr Val Ile Asp Glu Met Pro Glu Asn Pro Cys Phe His
        195                 200                 205

Glu Ile Ser Glu Leu His Gly Ser Gln Ser Glu Leu Asn Ser Leu Ser
    210                 215                 220

Glu Ser Ser Gly Lys Leu Asn Gly Asn Gly Ser Ser Glu Arg Arg Ser
225                 230                 235                 240

Asn Ala Asp Gln Ile Leu Val Asp Ala Glu Leu Glu Ile Glu Arg Leu
                245                 250                 255

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

Ser Phe Glu Thr Ala Gln His Asp Met Ser Ser Asn Ser Glu Ser Gly
        275                 280                 285

Asp Ile Ser Ile Leu Glu Lys Gln Asn Glu Glu Leu Arg Gln Lys Arg
    290                 295                 300

Arg Glu Leu Glu Glu Lys Asn Leu Glu Leu Asp Ala Ala Val Asp Gln
305                 310                 315                 320

Phe Lys Gly Ile Val Phe Glu Leu Thr Asn Glu Asn Asp Val Leu Arg
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340 345 350

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355 360 365

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

Ala Thr Leu Glu Asp Ala Asn Lys Asn Gly Ile Ala Gln Leu Arg Thr
405 410 415

Gln Val Gly Gly Leu Thr Ala Leu Asn Thr Glu Leu Lys Ala Ser Leu
420 425 430

Asp Ser Lys Lys Arg Cys Val Glu Gln Leu Glu Ile Gln Leu Ile Gln
435 440 445

His Lys Glu Lys Val Lys Glu Leu Glu Asp Arg Lys Asp Glu Leu Ile
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Glu Glu Arg Asn Arg Leu Glu Asn Gln Leu Ile Phe Lys Glu Ala Val
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Thr Pro Arg Ser Leu His Glu Ser Met Phe Glu Ala Gly Asn Leu Ser
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Phe Glu Pro Phe Ser Glu Lys Asn Thr Leu Pro Leu Glu Ile Glu Asn
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Lys Arg Leu Thr Glu Arg Ile Gln Glu Leu Glu Ser Leu Glu Pro Leu
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Lys Gly Glu Leu Ile Thr Leu Lys Ser Lys Asn Gly Val Leu Glu Glu
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Glu Lys Leu Phe Ala Thr Lys Gln Ile Glu Glu Leu Gln Gln Gln Ile
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Glu Asp Leu Gln Glu Asn Leu Leu Lys Asn Gln Glu His Ala Ser Gly
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Asp Val Val Gly Leu Lys Ile Gln Leu Glu Lys Ala Glu Val Glu Ala
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Gln Gln Met Arg Glu Ala Lys Met Arg Ala Glu Thr Asn Gln Ala Gln
595 600 605

Val Asp Glu Ile Leu Lys Lys Arg Thr Ala Glu Leu Glu Val Asn Ala
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Thr Ala Leu Gln Lys Ala Lys Ala Val Ile Asp Glu Leu Glu Tyr Asn
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Ser Arg Pro Val Ser Glu Asp Ser Met Thr Ser Val Gln Ala Phe Lys
645 650 655

Glu Met Lys Glu Glu Asn Glu Lys Leu Arg Gln Lys Val Glu Lys Leu
660 665 670

Glu Ile Glu Leu Asn Thr Val Thr Gln Gly Phe Glu Gln Glu Asn Arg
675 680 685

Leu Leu Thr Ser Ala Ser His Gln Gln Val Leu Asn Arg Ser Ile Asp
690 695 700

Glu Val Met Ser Met Arg Ala His Ala Gly Ser Glu Glu Pro Gln Thr
705 710 715 720

Leu Leu Asp Thr Gln Lys Met Ser Gly Ala Leu Pro Trp Arg Ser Leu
725 730 735

Ala Ser Glu Thr Arg Arg Glu Leu Pro Thr Ala Met Ala Ser Ile Leu
740 745 750

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Ser Ala Leu Asn Ala Pro Pro Asn Ala
770 775

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<211> 2187

<212> DNA

<213> Homo sapiens

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<210> 42
<211> 728
<212> PRT

<213> Homo sapiens

<400> 42

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            20                  25                  30

Asp Val Lys Gln Leu Thr Ser Gly Val Ala Met Ala Gln Val Leu His
        35                  40                  45

Gln Ile Asp Ala Ala Trp Phe Asn Glu Ser Trp Leu Ser Arg Ile Lys
    50                  55                  60

Glu Asp Val Gly Asp Asn Trp Arg Ile Lys Ala Ser Asn Val Lys Lys
65                  70                  75                  80

Val Leu Gln Gly Ile Met Ser Tyr Tyr His Glu Phe Leu Gly Gln Gln
                85                  90                  95

Ile Ser Glu Ala Leu Ile Pro Asp Leu Asn Gln Ile Thr Glu Cys Ser
            100                 105                 110

Asp Pro Val Glu Leu Gly Arg Leu Leu Gln Leu Ile Leu Gly Cys Ala
        115                 120                 125

Ile Asn Cys Glu Lys Lys Gln Glu His Ile Gln Asn Ile Met Thr Leu
    130                 135                 140

Glu Glu Ser Val Gln His Val Val Met Thr Ala Ile Gln Glu Leu Met
145                 150                 155                 160

Ser Lys Glu Ile Leu Ser Ser Pro Pro Asn Asp Ala Val Gly Glu Leu
                165                 170                 175

Glu Gln Gln Leu Lys Arg Ala Leu Glu Glu Leu Gln Glu Ala Leu Ala
            180                 185                 190

Glu Lys Glu Glu Leu Arg Gln Arg Cys Glu Glu Leu Asp Met Gln Val
        195                 200                 205

Thr Thr Leu Gln Asp Glu Lys Asn Ser Leu Val Ser Glu Asn Glu Met
    210                 215                 220

Met Asn Glu Lys Leu Asp Gln Leu Asp Gly Ser Phe Asp Asp Pro Asn
225                 230                 235                 240

Thr Val Val Ala Lys Lys Tyr Phe His Ala Gln Leu Gln Leu Glu Gln
                245                 250                 255
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Val His Cys Glu Glu Leu Glu Lys Gln Leu Ile Glu Phe Gln His Arg
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Asn Asp Glu Leu Thr Ser Leu Ala Glu Glu Thr Arg Ala Leu Lys Asp
    290                 295                 300

Glu Ile Asp Val Leu Arg Ala Thr Ser Asp Lys Ala Asn Lys Leu Glu
305                 310                 315                 320

Ser Thr Val Glu Ile Tyr Arg Gln Lys Leu Gln Asp Leu Asn Asp Leu
                325                 330                 335

Arg Lys Gln Val Lys Thr Leu Gln Glu Thr Asn Met Met Tyr Met His
            340                 345                 350

Asn Thr Val Ser Leu Glu Glu Glu Leu Lys Lys Ala Asn Ala Ala Arg
        355                 360                 365

Thr Gln Leu Glu Thr Tyr Lys Arg Gln Val Gln Asp Leu His Val Lys
    370                 375                 380

Leu Ser Ser Glu Ser Lys Arg Ala Asp Thr Leu Ala Phe Glu Met Lys
385                 390                 395                 400

Arg Leu Glu Glu Lys His Glu Ala Leu Leu Lys Glu Lys Glu Arg Leu
                405                 410                 415

Ile Glu Gln Arg Asp Thr Leu Lys Glu Thr Asn Glu Glu Leu Arg Cys
            420                 425                 430

Ser Gln Val Gln Gln Asp His Leu Asn Gln Thr Asp Ala Ser Ala Thr
        435                 440                 445

Lys Ser Tyr Glu Asn Leu Ala Ala Glu Ile Met Pro Val Glu Tyr Arg
    450                 455                 460

Glu Val Phe Ile Arg Leu Gln His Glu Asn Lys Met Leu Arg Leu Gln
465                 470                 475                 480

Gln Glu Gly Ser Glu Asn Glu Arg Ile Glu Glu Leu Gln Glu Gln Leu
                485                 490                 495

Glu Gln Lys His Arg Lys Met Asn Glu Leu Glu Thr Glu Gln Arg Leu
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Ser Lys Glu Arg Ile Arg Glu Leu Gln Gln Gln Ile Glu Asp Leu Gln
        515                 520                 525
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Lys Ser Leu Gln Glu Gln Gly Ser Lys Ser Glu Gly Glu Ser Ser Ser
530 535 540

Lys Leu Lys Gln Lys Leu Glu Ala His Met Glu Lys Leu Thr Glu Val
545 550 555 560

His Glu Glu Leu Gln Lys Lys Gln Glu Leu Ile Glu Asp Leu Gln Pro
565 570 575

Asp Ile Asn Gln Asn Val Gln Lys Ile Asn Glu Leu Glu Ala Ala Leu
580 585 590

Gln Lys Lys Asp Glu Asp Met Lys Ala Met Glu Glu Arg Tyr Lys Met
595 600 605

Tyr Leu Glu Lys Ala Arg Asn Val Ile Lys Thr Leu Asp Pro Lys Leu
610 615 620

Asn Pro Ala Ser Ala Glu Ile Met Leu Leu Arg Lys Gln Leu Ala Glu
625 630 635 640

Lys Glu Arg Arg Ile Glu Ile Leu Glu Ser Glu Cys Lys Val Ala Lys
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Phe Arg Asp Tyr Glu Glu Lys Leu Ile Val Ser Ala Trp Tyr Asn Lys
660 665 670

Ser Leu Ala Phe Gln Lys Leu Gly Met Glu Ser Arg Leu Val Ser Gly
675 680 685

Gly Gly Ala Cys Ser Asp Thr Gly Ala Cys Thr Pro Ala Arg Ser Phe
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Lys Val Pro Ala Thr Thr Ser Asp
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<211> 4597

<212> DNA

<213> Rattus norvegicus

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Leu Glu Lys Thr Val Pro Ser Glu Lys Ala Ser Gly Pro Pro Ser Ser
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Glu Thr Gln Glu Glu Phe Val Asp Asp Phe Arg Val Gly Glu Arg Val
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Trp Val Asn Gly Asn Lys Pro Gly Phe Ile Gln Phe Leu Gly Glu Thr
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Gln Phe Ala Pro Gly Gln Trp Ala Gly Ile Val Leu Asp Glu Pro Ile
85 90 95

Gly Lys Asn Asp Gly Ser Val Ala Gly Val Arg Tyr Phe Gln Cys Glu
100 105 110

Pro Leu Lys Gly Ile Phe Thr Arg Pro Ser Lys Leu Thr Arg Lys Val
115 120 125

Gln Ala Glu Asp Glu Ala Asn Gly Leu Gln Thr Ala His Ala Arg Ala
130 135 140

Ala Ser Pro Leu Ser Thr Ala Ala Ala Thr Met Val Ser Ser Ser Pro
145 150 155 160

Ala Thr Pro Ser Asn Ile Pro Gln Lys Pro Ser Gln Pro Val Ala Lys
165 170 175

Glu Thr Ser Ala Thr Pro Gln Ile Ser Asn Leu Thr Lys Thr Ala Ser
180 185 190

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Glu Ser Ile Ser Asn Leu Ser Glu Ala Gly Ser Val Lys Lys Gly Glu
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Arg Glu Leu Lys Ile Gly Asp Arg Val Leu Val Gly Gly Thr Lys Ala
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Gly Val Val Arg Phe Leu Gly Glu Thr Asp Phe Ala Lys Gly Glu Trp
225                 230                 235                 240

Cys Gly Val Glu Leu Asp Glu Pro Leu Gly Lys Asn Asp Gly Ala Val
                245                 250                 255

Ala Gly Thr Arg Tyr Phe Gln Cys Gln Pro Lys Tyr Gly Leu Phe Ala
            260                 265                 270

Pro Val His Lys Val Thr Lys Ile Gly Phe Pro Ser Thr Thr Pro Ala
        275                 280                 285

Lys Ala Lys Ala Ala Ala Val Arg Arg Val Met Ala Thr Thr Pro Ala
    290                 295                 300

Ser Leu Lys Arg Ser Pro Ser Ala Ser Ser Leu Ser Ser Met Ser Ser
305                 310                 315                 320

Val Ala Ser Ser Val Ser Ser Lys Pro Ser Arg Thr Gly Leu Leu Thr
                325                 330                 335

Glu Thr Ser Ser Arg Tyr Ala Arg Lys Ile Ser Gly Thr Thr Ala Leu
            340                 345                 350

Gln Glu Ala Leu Lys Glu Lys Gln Gln His Ile Glu Gln Leu Leu Ala
        355                 360                 365

Glu Arg Asp Leu Glu Arg Ala Glu Val Ala Lys Ala Thr Ser His Val
    370                 375                 380

Gly Glu Ile Glu Gln Glu Leu Ala Leu Ala Arg Asp Gly His Asp Gln
385                 390                 395                 400

His Val Leu Glu Leu Glu Ala Lys Met Asp Gln Leu Arg Thr Met Val
                405                 410                 415

Glu Ala Ala Asp Arg Glu Lys Val Glu Leu Leu Asn Gln Leu Glu Glu
            420                 425                 430

Glu Lys Arg Lys Val Glu Asp Leu Gln Phe Arg Val Glu Glu Glu Ser
        435                 440                 445

Ile Thr Lys Gly Asp Leu Glu Thr Gln Thr Lys Leu Glu His Ala Arg
    450                 455                 460
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Ile Lys Glu Leu Glu Gln Ser Leu Leu Phe Glu Lys Thr Lys Ala Asp
465                 470                 475                 480

Lys Leu Gln Arg Glu Leu Glu Asp Thr Arg Val Ala Thr Val Ser Glu
                485                 490                 495

Lys Ser Arg Ile Met Glu Leu Glu Lys Asp Leu Ala Leu Arg Val Gln
            500                 505                 510

Glu Val Ala Glu Leu Arg Arg Arg Leu Glu Ser Ser Lys Pro Pro Gly
        515                 520                 525

Asp Val Asp Met Ser Leu Ser Leu Leu Gln Glu Ile Ser Ala Leu Gln
    530                 535                 540

Glu Lys Leu Glu Val Thr His Thr Asp His Gln Asn Glu Val Thr Ser
545                 550                 555                 560

Leu Lys Asp His Phe Gly Thr Arg Glu Glu Met Phe Gln Lys Glu Ile
                565                 570                 575

Lys Ala Leu His Ala Ala Thr Glu Lys Leu Ser Lys Glu Asn Glu Ser
            580                 585                 590

Leu Arg Ser Lys Leu Asp His Ala Asn Lys Glu Asn Ser Asp Val Ile
        595                 600                 605

Ala Leu Trp Lys Ser Lys Leu Glu Thr Ala Ile Ala Ser His Gln Gln
    610                 615                 620

Ala Met Glu Glu Leu Lys Val Ser Phe Ser Lys Gly Ile Gly Thr Asp
625                 630                 635                 640

Ser Ala Glu Phe Ala Glu Leu Lys Thr Gln Ile Glu Arg Leu Arg Leu
                645                 650                 655

Asp Tyr Gln His Glu Ile Glu Ser Leu Gln Ser Lys Gln Asp Ser Glu
            660                 665                 670

Arg Ser Ala His Ala Lys Glu Met Glu Ser Met Lys Ala Lys Leu Met
        675                 680                 685

Lys Ile Ile Lys Glu Lys Glu Asp Ser Leu Glu Ala Val Lys Ala Arg
    690                 695                 700

Leu Asp Thr Ala Glu Asp Gln His Leu Val Glu Met Glu Glu Met Leu
705                 710                 715                 720

Ser Lys Leu Gln Glu Ala Glu Ile Lys Lys Glu Lys Phe Ala Ser Ala
                725                 730                 735
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Ser Glu Glu Ala Val Ser Thr Gln Thr Ser Met Gln Asp Thr Val Asn
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Lys Leu His Gln Lys Glu Glu Gln Phe Asn Met Leu Ser Ser Glu Leu
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Glu Lys Leu Arg Glu Asn Leu Thr Asp Met Glu Ala Lys Phe Lys Glu
    770                 775                 780

Lys Asp Glu Arg Glu Asp Gln Leu Val Lys Ala Lys Glu Lys Leu Glu
785                 790                 795                 800

Asn Asp Ile Ala Glu Ile Met Lys Met Ser Gly Asp Asn Ser Ser Gln
                805                 810                 815

Leu Thr Lys Met Asn Asp Glu Leu Arg Leu Lys Glu Arg Ser Val Glu
            820                 825                 830

Glu Leu Gln Leu Lys Leu Thr Lys Ala Asn Glu Asn Ala Ser Leu Leu
        835                 840                 845

Gln Lys Ser Ile Gly Glu Val Thr Leu Lys Ala Glu Gln Ser Gln Gln
    850                 855                 860

Glu Ala Ala Lys Lys His Glu Glu Glu Lys Lys Glu Leu Glu Asn Lys
865                 870                 875                 880

Leu Leu Glu Leu Glu Lys Lys Met Glu Thr Ser His Tyr Gln Cys Gln
                885                 890                 895

Asp Leu Lys Ala Lys Tyr Glu Lys Ala Ser Ser Glu Thr Lys Ile Lys
            900                 905                 910

His Glu Glu Ile Leu Gln Asn Phe Gln Lys Met Leu Val Asp Thr Glu
        915                 920                 925

Asp Lys Leu Lys Ala Ala Gln Glu Ala Asn Arg Asp Leu Met Gln Asp
    930                 935                 940

Met Glu Glu Leu Lys Ser Gln Ala Asp Lys Ala Lys Ala Ala Gln Thr
945                 950                 955                 960

Ala Glu Asp Ala Met Gln Ile Met Glu Gln Met Thr Lys Glu Lys Thr
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Glu Thr Leu Ala Ser Leu Glu Asp Thr Lys Gln Thr Asn Ala Lys Leu
            980                 985                 990

Gln Ser Glu Leu Asp Thr Leu Lys  Glu Asn Asn Leu Lys  Thr Val Glu
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Glu Leu  Asn Lys Ser Lys Glu  Leu Leu Asn Glu Glu  Asn Gln Lys
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Ala Gln Lys Ser Gln Gln Leu Ser Ala Leu Gln Glu Glu Asn Val
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Lys Leu Ala Glu Glu Leu Gly Arg Thr Arg Asp Glu Val Thr Ser
1055 1060 1065

His Gln Lys Leu Glu Glu Glu Arg Ser Val Leu Asn Asn Gln Leu
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Leu Glu Met Lys Lys Ser Leu Pro Ser Asn Thr Leu Arg Glu Ser
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Glu Tyr Arg Lys Asp Ala Asp Glu Glu Lys Ala Ser Leu Gln Lys
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Ser Ile Ser Leu Thr Ser Ala Leu Leu Thr Glu Lys Asp Ala Glu
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Leu Glu Lys Leu Arg Asn Glu Val Thr Val Leu Arg Gly Glu Asn
1130 1135 1140

Ala Ser Ala Lys Ser Leu His Ser Val Val Gln Thr Leu Glu Ser
1145 1150 1155

Asp Lys Val Lys Leu Glu Leu Lys Val Lys Asn Leu Glu Leu Gln
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Leu Lys Glu Asn Lys Arg Gln Leu Ser Ser Ser Ser Gly Asn Thr
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Asp Val Gln Thr Glu Glu Asp Glu Arg Ala Gln Glu Ser Gln Gln
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Met Ile Asp Phe Leu Asn Ser Val Ile Val Asp Leu Gln Arg Lys
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Asn Gln Asp Leu Lys Met Lys Val Glu Met Met Ser Glu Gly Ala
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Leu Asn Gly Asn Gly Glu Asp Pro Asn Ser Tyr Asp Ser Asp Asp
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Gln Glu Lys Gln Ser Lys Lys Lys Pro Arg Leu Phe Cys Asp Ile
1250 1255 1260

Cys Asp Cys Phe Asp Leu His Asp Thr Glu Asp Cys Pro Thr Gln
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Ala Gln Met Ser Glu Asp Pro Pro His Ser Thr His His Gly Ser
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Arg Ser Glu Glu Arg Pro Tyr Cys Glu Ile Cys Glu Met Phe Gly
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His Trp Ala Thr Asn Cys Asn Asp Asp Glu Thr Phe
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35 40 45

Ala Thr Leu Phe Ala Thr Gly Lys Trp Val Gly Val Ile Leu Asp Glu
50 55 60

Ala Lys Gly Lys Asn Asp Gly Thr Val Gln Gly Arg Lys Tyr Phe Thr
65 70 75 80

Cys Asp Glu Gly His Gly Ile Phe Val Arg Gln Ser Gln Ile Gln Val
85 90 95

Phe Glu Asp Gly Ala Asp Thr Thr Ser Pro Glu Thr Pro Asp Ser Ser
100 105 110

Ala Ser Lys Val Leu Lys Arg Glu Gly Ala Asp Ala Ala Ala Lys Thr
115 120 125

Ser Lys Leu Arg Gly Leu Lys Pro Lys Lys Ala Pro Thr Ala Arg Lys
130 135 140

Thr Thr Thr Arg Arg Pro Lys Pro Thr Arg Pro Ala Ser Thr Gly Val
145 150 155 160

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Ala Gly Pro Ser Ser Ser Leu Gly Pro Ser Gly Ser Ala Ser Ala Gly
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Glu Leu Ser Ser Ser Glu Pro Ser Thr Pro Ala Gln Thr Pro Leu Ala
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Ala Pro Ile Ile Pro Thr Pro Ala Leu Thr Ser Pro Gly Ala Ala Pro
        195                 200                 205

Pro Leu Pro Ser Pro Ser Lys Glu Glu Glu Gly Leu Arg Ala Gln Val
    210                 215                 220

Arg Asp Leu Glu Glu Lys Leu Glu Thr Leu Arg Leu Lys Arg Ser Glu
225                 230                 235                 240

Asp Lys Ala Lys Leu Lys Glu Leu Glu Lys His Lys Ile Gln Leu Glu
                245                 250                 255

Gln Val Gln Glu Trp Lys Ser Lys Met Gln Glu Gln Gln Ala Asp Leu
            260                 265                 270

Gln Arg Arg Leu Lys Glu Ala Arg Lys Glu Ala Lys Glu Ala Leu Glu
        275                 280                 285

Ala Lys Glu Arg Tyr Met Glu Glu Met Ala Asp Thr Ala Asp Ala Ile
    290                 295                 300

Glu Met Ala Thr Leu Asp Lys Glu Met Ala Glu Glu Arg Ala Glu Ser
305                 310                 315                 320

Leu Gln Gln Glu Val Glu Ala Leu Lys Glu Arg Val Asp Glu Leu Thr
                325                 330                 335

Thr Asp Leu Glu Ile Leu Lys Ala Glu Ile Glu Glu Lys Gly Ser Asp
            340                 345                 350

Gly Ala Ala Ser Ser Tyr Gln Leu Lys Gln Leu Glu Glu Gln Asn Ala
        355                 360                 365

Arg Leu Lys Asp Ala Leu Val Arg Met Arg Asp Leu Ser Ser Ser Glu
    370                 375                 380

Lys Gln Glu His Val Lys Leu Gln Lys Leu Met Glu Lys Lys Asn Gln
385                 390                 395                 400

Glu Leu Glu Val Val Arg Gln Gln Arg Glu Arg Leu Gln Glu Glu Leu
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Ser Gln Ala Glu Ser Thr Ile Asp Glu Leu Lys Glu Gln Val Asp Ala
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Ala Leu Gly Ala Glu Glu Met Val Glu Met Leu Thr Asp Arg Asn Leu
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Asn Leu Glu Glu Lys Val Arg Glu Leu Arg Glu Thr Val Gly Asp Leu
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Glu Ala Met Asn Glu Met Asn Asp Glu Leu Gln Glu Asn Ala Arg Glu
465 470 475 480

Thr Glu Leu Glu Leu Arg Glu Gln Leu Asp Met Ala Gly Ala Arg Val
485 490 495

Arg Glu Ala Gln Lys Arg Val Glu Ala Ala Gln Glu Thr Val Ala Asp
500 505 510

Tyr Gln Gln Thr Ile Lys Lys Tyr Arg Gln Leu Thr Ala His Leu Gln
515 520 525

Asp Val Asn Arg Glu Leu Thr Asn Gln Gln Glu Ala Ser Val Glu Arg
530 535 540

Gln Gln Gln Pro Pro Pro Glu Thr Phe Asp Phe Lys Ile Lys Phe Ala
545 550 555 560

Glu Thr Lys Ala His Ala Lys Ala Ile Glu Met Glu Leu Arg Gln Met
565 570 575

Glu Val Ala Gln Ala Asn Arg His Met Ser Leu Leu Thr Ala Phe Met
580 585 590

Pro Asp Ser Phe Leu Arg Pro Gly Gly Asp His Asp Cys Val Leu Val
595 600 605

Leu Leu Leu Met Pro Arg Leu Ile Cys Lys Ala Glu Leu Ile Arg Lys
610 615 620

Gln Ala Gln Glu Lys Phe Asp Leu Ser Glu Asn Cys Ser Glu Arg Pro
625 630 635 640

Gly Leu Arg Gly Ala Ala Gly Glu Gln Leu Ser Phe Ala Ala Gly Leu
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Val Tyr Ser Leu Ser Leu Leu Gln Ala Thr Leu His Arg Tyr Glu His
660 665 670

Ala Leu Ser Gln Cys Ser Val Asp Val Tyr Lys Lys Val Gly Ser Leu
675 680 685

Tyr Pro Glu Met Ser Ala His Glu Arg Ser Leu Asp Phe Leu Ile Glu
690 695 700

Leu Leu His Lys Asp Gln Leu Asp Glu Thr Val Asn Val Glu Pro Leu

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Thr Lys Ala Ile Lys Tyr Tyr Gln His Leu Tyr Ser Ile His Leu Ala
725 730 735

Glu Gln Pro Glu Asp Ser Thr Met Gln Leu Ala Asp His Ile Lys Phe
740 745 750

Thr Gln Ser Ala Leu Asp Cys Met Gly Val Glu Val Gly Arg Leu Arg
755 760 765

Ala Phe Leu Gln Gly Gly Gln Glu Ala Thr Asp Ile Ala Leu Leu Leu
770 775 780

Arg Asp Leu Glu Thr Ser Cys Ser Asp Thr Arg Gln Phe Cys Lys Lys
785 790 795 800

Ile Arg Arg Arg Met Pro Gly Thr Asp Ala Pro Gly Ile Pro Ala Ala
805 810 815

Leu Ala Phe Gly Ser Gln Val Ser Asp Thr Leu Leu Asp Cys Arg Lys
820 825 830

His Leu Thr Trp Val Val Ala Val Leu Gln Glu Val Ala Ala Ala Ala
835 840 845

Ala Gln Leu Ile Ala Pro Leu Ala Glu Asn Glu Gly Leu Pro Val Ala
850 855 860

Ala Leu Glu Glu Leu Ala Phe Lys Ala Ser Glu Gln Ile Tyr Gly Ser
865 870 875 880

Pro Ser Ser Ser Pro Tyr Glu Cys Leu Arg Gln Ser Cys Thr Ile Leu
885 890 895

Ile Ser Thr Met Asn Lys Leu Ala Thr Ala Met Gln Glu Gly Glu Tyr
900 905 910

Asp Ala Glu Arg Pro Pro Ser Lys Pro Pro Pro Val Glu Leu Arg Ala
915 920 925

Ala Ala Leu Arg Ala Glu Ile Thr Asp Ala Glu Gly Leu Gly Leu Lys
930 935 940

Leu Glu Asp Arg Glu Thr Val Ile Lys Glu Leu Lys Lys Ser Leu Lys
945 950 955 960

Ile Lys Gly Glu Glu Leu Ser Glu Ala Asn Val Arg Leu Ser Leu Leu
965 970 975

Glu Lys Lys Leu Asp Ser Ala Ala Lys Asp Ala Asp Glu Arg Ile Glu
980 985 990

Lys Val Gln Thr Arg Leu Asp Glu Thr Gln Thr Leu Leu Arg Lys Lys
995 1000 1005

Glu Lys Asp Phe Glu Glu Thr Met Asp Ala Leu Gln Ala Asp Ile
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Asp Gln Leu Glu Ala Glu Lys Ala Glu Leu Lys Gln Arg Leu Asn
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Ser Gln Ser Lys Arg Thr Ile Glu Gly Leu Arg Gly Pro Pro Pro
1040 1045 1050

Ser Gly Ile Ala Thr Leu Val Ser Gly Ile Ala Gly Glu Glu Pro
1055 1060 1065

Gln Arg Gly Gly Ala Pro Gly Gln Ala Pro Gly Ala Leu Pro Gly
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Pro Gly Leu Val Lys Asp Ser Pro Leu Leu Leu Gln Gln Ile Ser
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Ala Met Arg Leu His Ile Ser Gln Leu Gln His Glu Asn Ser Ile
1100 1105 1110

Leu Arg Gly Ala Gln Met Lys Ala Ser Leu Ala Ala Leu Pro Pro
1115 1120 1125

Leu His Val Ala Lys Leu Ser Leu Pro Pro His Glu Gly Pro Gly
1130 1135 1140

Gly Asn Leu Val Ala Gly Ala Leu Tyr Arg Lys Thr Ser Gln Leu
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Leu Glu Lys Leu Asn Gln Leu Ser Thr His Thr His Val Val Asp
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Ile Thr Arg Ser Ser Pro Ala Ala Lys Ser Pro Ser Ala Gln Leu
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Met Glu Gln Val Ala Gln Leu Lys Ser Leu Ser Asp Thr Ile Glu
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Phe Leu Arg Ala Lys Glu Glu Gln Gln Asp Asp Thr Val Tyr Met
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Gly Lys Val Thr Phe Ser Cys Ala Ala Gly Leu Gly Gln Arg His
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<213> Drosophila melanogaster

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Pro Lys Ser Gly Pro Pro Pro Arg Glu Ala Thr Ser Met Ser Arg Glu
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Thr His Phe Ala Ala Gly Glu Trp Ala Gly Val Val Leu Asp Glu Pro
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Ser Thr Pro Val Lys Pro Ile Leu Ala Thr Pro Lys Ser Gln Phe Ser
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Val Tyr Lys Glu Lys Ile His Asp Leu Glu Ser Lys Ile Thr Lys Leu
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Lys Thr Leu Asn Asp Lys Glu Gln Leu Glu Lys Gln Ile Ser Asp Leu
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Thr Lys Leu Lys Ser Glu Val Gly Glu Thr Gln Ala Ala Leu Ser Ser
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Cys His Thr Asp Val Glu Ser Lys Thr Lys Gln Leu Glu Ala Ala Asn
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Ala Ala Leu Glu Lys Val Asn Lys Glu Tyr Ala Glu Ser Arg Ala Glu
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Ala Ser Asp Leu Gln Asp Lys Val Lys Glu Ile Thr Asp Thr Leu His
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Gln Thr  Lys Leu Lys Ala Glu  Gly Glu Arg Lys Glu  Lys Ser Phe
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Glu Lys  Ser Glu Thr Asn His  Ile Phe Glu Leu Phe  Glu Met Glu
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Ala Asp  Met Asn Ser Glu Arg  Leu Ile Glu Lys Val  Thr Gly Ile
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Lys Gln  Lys Glu Glu Leu Val  Gln Asn Leu Glu Glu  Lys Val Arg
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Glu Ser  Ser Ser Ile Ile Glu  Ala Gln Asn Thr Lys  Leu Asn Glu
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Val Lys  Val Leu Glu Glu Lys  Leu Gln Ala Ala Thr  Ser Gln Leu
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Gln Tyr Arg Glu Ser Val Ile Ala Ser Gly Leu Lys Pro Leu Leu Asn
50 55 60

Thr Leu Lys Arg Asp Tyr Met Asp Glu Asp Ser Val Lys Ala Ile Leu
65 70 75 80

Glu Thr Ile Leu Ile Leu Phe Ile Arg Gly Asp Gly His Asp Asp Leu
85 90 95

Thr Arg Gly Trp Ile Ser Gln Gln Ser Arg Leu Gln Asn Gly Lys Tyr
100 105 110

Pro Ser Pro Leu Val Met Lys Gln Glu Lys Glu Gln Val Asp Gln Phe
115 120 125

Ser Leu Trp Ile Ala Asp Ala Leu Thr Gln Ser Glu Asp Leu Ile His
130 135 140

Leu Leu Val Glu Phe Trp Glu Ile Asp Asn Phe His Ile Arg Leu Tyr
145 150 155 160

Thr Ile Gln Leu Leu Glu Ala Val Met Ala Thr Arg Pro Leu Lys Ala
165 170 175

Arg Ser Ala Leu Ile Ser Leu Pro Thr Ser Ile Ser Thr Met Val Ser
180 185 190

Leu Leu Asp Asp Met His Glu Pro Ile Arg Asp Glu Ala Ile Leu Leu
195 200 205

Leu Met Ala Val Val Asn Asp Ser Pro His Val Gln Lys Leu Val Ala
210 215 220

Phe Glu Asn Ile Phe Glu Arg Leu Phe Ser Ile Ile Glu Glu Glu Gly
225 230 235 240

Gly Leu Arg Gly Ser Leu Val Val Asn Asp Cys Leu Ser Leu Ile Asn
245 250 255

Asn Ile Leu Lys Tyr Asn Thr Ser Asn Gln Thr Leu Phe Leu Glu Thr
260 265 270

Gly Asn Leu Pro Lys Leu Ala His Leu Leu Ser Glu Pro Ile Ser Gln
275 280 285

Asp Glu Val Phe Phe Trp Asn Asp Gln Arg Ile Val Asn Ile Asn Thr
290 295 300

Ala Leu Asp Ile Val Ser Leu Thr Val Glu Pro Gly Asn Thr Val Thr
305 310 315 320

Thr Lys His Gln Asn Ala Leu Leu Asp Ser Ser Val Leu Met Val Val
325 330 335

Leu Arg Leu Ala Phe Phe His Asn Ile Pro Lys Lys Val Arg Pro Val
340 345 350

Ala Leu Leu Thr Ala Ala Asn Met Val Arg Ser Asn Glu His Ala Gln
355 360 365

Leu Glu Phe Ser Lys Ile Asp Val Pro Tyr Phe Asp Pro Ser Leu Pro
370 375 380

Val Asn Ser Thr Ala Asn Gly Gly Pro Ile Lys Leu Ile Pro Val Val
385 390 395 400

Ser Ile Leu Ile Asn Trp Met Leu Tyr Ala Asn Ser Val His Thr Phe
405 410 415

Asp Thr Arg Val Ala Cys Ser Arg Leu Leu Lys Ala Tyr Phe Met Asp
420 425 430

Asn Phe Asp Leu Gln Arg Asp Phe Leu Leu Lys Gln Val Gln Leu Cys
435 440 445

Asn Asn Ser Thr Asn Asn Val Gly Asp Asn Ala Lys Glu Asn Gly Gly
450 455 460

Ser Asn Lys Ser Asp Lys Glu Ser Asp Ser Asp Lys Asp Thr Asp Gly
465 470 475 480

Lys Asp Gly Thr Glu Tyr Glu Gly Ser Phe Lys Ala Asn Leu Phe Glu
485 490 495

Val Leu Leu Asn Tyr Asp Ala Glu Leu Asn Leu Asn Pro Phe Lys Leu
500 505 510

Phe Phe Thr Thr Asp Ile Phe Met Phe Phe Phe Gln Gln Asp His Lys
515 520 525

Tyr Ser Glu Glu Leu Arg Glu Ile Thr Arg Asn Val Thr Thr Gly Asn
530 535 540

Asp Leu Glu Asp Glu Glu Pro Leu Lys Ala Ile Gln Thr Ile Ser Glu
545 550 555 560

Leu Leu Thr Thr Ser Leu Thr Ala Ala Asp Ile Arg Ile Pro Ile Ser
565 570 575

Tyr Leu Thr Phe Leu Ile Tyr Trp Leu Phe Gly Asp Phe Lys Ala Thr
580 585 590

Asn Asp Phe Leu Ser Asp Lys Ser Val Ile Lys Ser Leu Leu Ser Phe
595 600 605

Ser Tyr Gln Ile Gln Asp Glu Asp Val Thr Ile Lys Cys Leu Val Thr
610 615 620

Met Leu Leu Gly Val Ala Tyr Glu Phe Ser Ser Lys Glu Ser Pro Phe
625 630 635 640

Pro Arg Lys Glu Tyr Phe Glu Phe Ile Thr Lys Thr Leu Gly Lys Asp
645 650 655

Asn Tyr Ala Ser Arg Ile Lys Gln Phe Lys Lys Asp Ser Tyr Phe Ser
660 665 670

Lys Val Asp Met Asn Glu Asp Ser Ile Leu Thr Pro Glu Leu Asp Glu
675 680 685

Thr Gly Leu Pro Lys Val Tyr Phe Ser Thr Tyr Phe Ile Gln Leu Phe
690 695 700

Asn Glu Asn Ile Tyr Arg Ile Arg Thr Ala Leu Ser His Asp Pro Asp
705 710 715 720

Glu Glu Pro Ile Asn Lys Ile Ser Phe Glu Glu Val Glu Lys Leu Gln
725 730 735

Arg Gln Cys Thr Lys Leu Lys Gly Glu Ile Thr Ser Leu Gln Thr Glu
740 745 750

Thr Glu Ser Thr His Glu Asn Leu Thr Glu Lys Leu Ile Ala Leu Thr
755 760 765

Asn Glu His Lys Glu Leu Asp Glu Lys Tyr Gln Ile Leu Asn Ser Ser

770 775 780

His Ser Ser Leu Lys Glu Asn Phe Ser Ile Leu Glu Thr Glu Leu Lys
785 790 795 800

Asn Val Arg Asp Ser Leu Asp Glu Met Thr Gln Leu Arg Asp Val Leu
805 810 815

Glu Thr Lys Asp Lys Glu Asn Gln Thr Ala Leu Leu Glu Tyr Lys Ser
820 825 830

Thr Ile His Lys Gln Glu Asp Ser Ile Lys Thr Leu Glu Lys Gly Leu
835 840 845

Glu Thr Ile Leu Ser Gln Lys Lys Lys Ala Glu Asp Gly Ile Asn Lys
850 855 860

Met Gly Lys Asp Leu Phe Ala Leu Ser Arg Glu Met Gln Ala Val Glu
865 870 875 880

Glu Asn Cys Lys Asn Leu Gln Lys Glu Lys Asp Lys Ser Asn Val Asn
885 890 895

His Gln Lys Glu Thr Lys Ser Leu Lys Glu Asp Ile Ala Ala Lys Ile
900 905 910

Thr Glu Ile Lys Ala Ile Asn Glu Asn Leu Glu Glu Met Lys Ile Gln
915 920 925

Cys Asn Asn Leu Ser Lys Glu Lys Glu His Ile Ser Lys Glu Leu Val
930 935 940

Glu Tyr Lys Ser Arg Phe Gln Ser His Asp Asn Leu Val Ala Lys Leu
945 950 955 960

Thr Glu Lys Leu Lys Ser Leu Ala Asn Asn Tyr Lys Asp Met Gln Ala
965 970 975

Glu Asn Glu Ser Leu Ile Lys Ala Val Glu Glu Ser Lys Asn Glu Ser
980 985 990

Ser Ile Gln Leu Ser Asn Leu Gln Asn Lys Ile Asp Ser Met Ser Gln
995 1000 1005

Glu Lys Glu Asn Phe Gln Ile Glu Arg Gly Ser Ile Glu Lys Asn
1010 1015 1020

Ile Glu Gln Leu Lys Lys Thr Ile Ser Asp Leu Glu Gln Thr Lys
1025 1030 1035

Glu Glu Ile Ile Ser Lys Ser Asp Ser Ser Lys Asp Glu Tyr Glu
1040 1045 1050

Ser Gln Ile Ser Leu Leu Lys Glu Lys Leu Glu Thr Ala Thr Thr
1055 1060 1065

Ala Asn Asp Glu Asn Val Asn Lys Ile Ser Glu Leu Thr Lys Thr
1070 1075 1080

Arg Glu Glu Leu Glu Ala Glu Leu Ala Ala Tyr Lys Asn Leu Lys
1085 1090 1095

Asn Glu Leu Glu Thr Lys Leu Glu Thr Ser Glu Lys Ala Leu Lys
1100 1105 1110

Glu Val Lys Glu Asn Glu Glu His Leu Lys Glu Glu Lys Ile Gln
1115 1120 1125

Leu Glu Lys Glu Ala Thr Glu Thr Lys Gln Gln Leu Asn Ser Leu
1130 1135 1140

Arg Ala Asn Leu Glu Ser Leu Glu Lys Glu His Glu Asp Leu Ala
1145 1150 1155

Ala Gln Leu Lys Lys Tyr Glu Glu Gln Ile Ala Asn Lys Glu Arg
1160 1165 1170

Gln Tyr Asn Glu Glu Ile Ser Gln Leu Asn Asp Glu Ile Thr Ser
1175 1180 1185

Thr Gln Gln Glu Asn Glu Ser Ile Lys Lys Lys Asn Asp Glu Leu
1190 1195 1200

Glu Gly Glu Val Lys Ala Met Lys Ser Thr Ser Glu Glu Gln Ser
1205 1210 1215

Asn Leu Lys Lys Ser Glu Ile Asp Ala Leu Asn Leu Gln Ile Lys
1220 1225 1230

Glu Leu Lys Lys Lys Asn Glu Thr Asn Glu Ala Ser Leu Leu Glu
1235 1240 1245

Ser Ile Lys Ser Val Glu Ser Glu Thr Val Lys Ile Lys Glu Leu
1250 1255 1260

Gln Asp Glu Cys Asn Phe Lys Glu Lys Glu Val Ser Glu Leu Glu
1265 1270 1275

Asp Lys Leu Lys Ala Ser Glu Asp Lys Asn Ser Lys Tyr Leu Glu
1280 1285 1290

Leu Gln Lys Glu Ser Glu Lys Ile Lys Glu Glu Leu Asp Ala Lys
1295 1300 1305

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Thr Thr  Glu Leu Lys Ile Gln  Leu Glu Lys Ile Thr  Asn Leu Ser
    1310                 1315                 1320

Lys Ala  Lys Glu Lys Ser Glu  Ser Glu Leu Ser Arg  Leu Lys Lys
    1325                 1330                 1335

Thr Ser  Ser Glu Glu Arg Lys  Asn Ala Glu Glu Gln  Leu Glu Lys
    1340                 1345                 1350

Leu Lys  Asn Glu Ile Gln Ile  Lys Asn Gln Ala Phe  Glu Lys Glu
    1355                 1360                 1365

Arg Lys  Leu Leu Asn Glu Gly  Ser Ser Thr Ile Thr  Gln Glu Tyr
    1370                 1375                 1380

Ser Glu  Lys Ile Asn Thr Leu  Glu Asp Glu Leu Ile  Arg Leu Gln
    1385                 1390                 1395

Asn Glu  Asn Glu Leu Lys Ala  Lys Glu Ile Asp Asn  Thr Arg Ser
    1400                 1405                 1410

Glu Leu  Glu Lys Val Ser Leu  Ser Asn Asp Glu Leu  Leu Glu Glu
    1415                 1420                 1425

Lys Gln  Asn Thr Ile Lys Ser  Leu Gln Asp Glu Ile  Leu Ser Tyr
    1430                 1435                 1440

Lys Asp  Lys Ile Thr Arg Asn  Asp Glu Lys Leu Leu  Ser Ile Glu
    1445                 1450                 1455

Arg Asp  Asn Lys Arg Asp Leu  Glu Ser Leu Lys Glu  Gln Leu Arg
    1460                 1465                 1470

Ala Ala  Gln Glu Ser Lys Ala  Lys Val Glu Glu Gly  Leu Lys Lys
    1475                 1480                 1485

Leu Glu  Glu Glu Ser Ser Lys  Glu Lys Ala Glu Leu  Glu Lys Ser
    1490                 1495                 1500

Lys Glu  Met Met Lys Lys Leu  Glu Ser Thr Ile Glu  Ser Asn Glu
    1505                 1510                 1515

Thr Glu  Leu Lys Ser Ser Met  Glu Thr Ile Arg Lys  Ser Asp Glu
    1520                 1525                 1530

Lys Leu  Glu Gln Ser Lys Lys  Ser Ala Glu Glu Asp  Ile Lys Asn
    1535                 1540                 1545

Leu Gln  His Glu Lys Ser Asp  Leu Ile Ser Arg Ile  Asn Glu Ser
    1550                 1555                 1560
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Glu Lys Asp Ile Glu Glu Leu Lys Ser Lys Leu Arg Ile Glu Ala
1565 1570 1575

Lys Ser Gly Ser Glu Leu Glu Thr Val Lys Gln Glu Leu Asn Asn
1580 1585 1590

Ala Gln Glu Lys Ile Arg Ile Asn Ala Glu Glu Asn Thr Val Leu
1595 1600 1605

Lys Ser Lys Leu Glu Asp Ile Glu Arg Glu Leu Lys Asp Lys Gln
1610 1615 1620

Ala Glu Ile Lys Ser Asn Gln Glu Glu Lys Glu Leu Leu Thr Ser
1625 1630 1635

Arg Leu Lys Glu Leu Glu Gln Glu Leu Asp Ser Thr Gln Gln Lys
1640 1645 1650

Ala Gln Lys Ser Glu Glu Glu Arg Arg Ala Glu Val Arg Lys Phe
1655 1660 1665

Gln Val Glu Lys Ser Gln Leu Asp Glu Lys Ala Met Leu Leu Glu
1670 1675 1680

Thr Lys Tyr Asn Asp Leu Val Asn Lys Glu Gln Ala Trp Lys Arg
1685 1690 1695

Asp Glu Asp Thr Val Lys Lys Thr Thr Asp Ser Gln Arg Gln Glu
1700 1705 1710

Ile Glu Lys Leu Ala Lys Glu Leu Asp Asn Leu Lys Ala Glu Asn
1715 1720 1725

Ser Lys Leu Lys Glu Ala Asn Glu Asp Arg Ser Glu Ile Asp Asp
1730 1735 1740

Leu Met Leu Leu Val Thr Asp Leu Asp Glu Lys Asn Ala Lys Tyr
1745 1750 1755

Arg Ser Lys Leu Lys Asp Leu Gly Val Glu Ile Ser Ser Asp Glu
1760 1765 1770

Glu Asp Asp Glu Glu Asp Asp Glu Glu Asp Glu Glu Glu Gly Gln
1775 1780 1785

Val Ala
1790

<210> 51

<211> 666

<212> DNA

<213> Caenorhabditis elegans

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gaatctattc aaaaacttcg ggaaacagag gagatgcttg agaagaaaca agaattcttg 120
gagaaaaaag ttatcgacga aaagcaaaat gccgtgaagt atggaacgaa aaacaagcga 180
atggctctcc agtgtttgaa tagaaagaga aatttcgaga agcagttggc ccatattgac 240
ggagttttgt ctactatcgg atatcagaga gaagccctcg aaaatgcttc aacgaatgct 300
gaagttctca atgttatggg aactgctagc aaggcgttga aagcggctca taacaacatg 360
gatatcgacc aagttcatga tttgatggaa gacatagctg agcaacaaga agtggcaaac 420
gaaatcgctg aagctatttc aaaccctgtc ggcttcagca ccgcagttga cgatgacgat 480
ttgatgcgcg agttggaggc tcttgaacag gaagaacttg acaaagaatt gcttgatgcg 540
agagctccac cagtcacgct tccggatact ccaaatattg cacttccagc agttccggct 600
tccagaccga gagcgaaaga agctgacaag gatctcgaag acctcgaaag ctgggcaaac 660
gcgtga 666

<210> 52
<211> 221
<212> PRT
<213> Caenorhabditis elegans

<400> 52
Met Ser Leu Phe Gly Lys Ile Phe Gly Gly Arg Lys Gln Glu Ala Pro
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Ser Thr Pro Gln Glu Ser Ile Gln Lys Leu Arg Glu Thr Glu Glu Met
20 25 30

Leu Glu Lys Lys Gln Glu Phe Leu Glu Lys Lys Val Ile Asp Glu Lys
35 40 45

Gln Asn Ala Val Lys Tyr Gly Thr Lys Asn Lys Arg Met Ala Leu Gln
50 55 60

Cys Leu Asn Arg Lys Arg Asn Phe Glu Lys Gln Leu Ala His Ile Asp
65 70 75 80

Gly Val Leu Ser Thr Ile Gly Tyr Gln Arg Glu Ala Leu Glu Asn Ala
85 90 95

Ser Thr Asn Ala Glu Val Leu Asn Val Met Gly Thr Ala Ser Lys Ala
100 105 110

Leu Lys Ala Ala His Asn Asn Met Asp Ile Asp Gln Val His Asp Leu
115 120 125

Met Glu Asp Ile Ala Glu Gln Gln Glu Val Ala Asn Glu Ile Ala Glu
130 135 140

Ala Ile Ser Asn Pro Val Gly Phe Ser Thr Ala Val Asp Asp Asp Asp
145 150 155 160

Leu Met Arg Glu Leu Glu Ala Leu Glu Gln Glu Glu Leu Asp Lys Glu
165 170 175

Leu Leu Asp Ala Arg Ala Pro Pro Val Thr Leu Pro Asp Thr Pro Asn
180 185 190

Ile Ala Leu Pro Ala Val Pro Ala Ser Arg Pro Arg Ala Lys Glu Ala
195 200 205

Asp Lys Asp Leu Glu Asp Leu Glu Ser Trp Ala Asn Ala
210 215 220

<210> 53

<211> 675

<212> DNA

<213> Homo sapiens

<400> 53
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gagttcctgg agaagaaaat cgagcaggag ctgacggccg ccaagaagca cggcaccaaa 180

aacaagcgcg cggccctcca ggcactgaag cgtaagaaga ggtatgagaa gcagctggcg 240

cagatcgacg gcacattatc aaccatcgag ttccagcggg aggccctgga gaatgccaac 300

accaacaccg aggtgctcaa gaacatgggc tatgccgcca aggccatgaa ggcggcccat 360

gacaacatgg acatcgataa agttgatgag ttaatgcagg acattgctga ccagcaagaa 420

cttgcagagg agatttcaac agcaatttcg aaacctgtag ggtttggaga agagtttgac 480

gaggatgagc tcatggcgga attagaagaa ctagaacagg aggaactaga caagaatttg 540

ctggaaatca gtggacccga aacagtccct ctaccaaatg ttccctctat agccctacca 600

tcaaaacccg ccaagaagaa agaagaggag gacgacgaca tgaaggaatt ggagaactgg 660

gctggatcca tgtaa 675

<210> 54

<211> 224

<212> PRT

<213> Homo sapiens

<400> 54

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Met Ser Val Phe Gly Lys Leu Phe Gly Ala Gly Gly Gly Lys Ala Gly
1               5                  10                  15

Lys Gly Gly Pro Thr Pro Gln Glu Ala Ile Gln Arg Leu Arg Asp Thr
            20                  25                  30

Glu Glu Met Leu Ser Lys Lys Gln Glu Phe Leu Glu Lys Lys Ile Glu
        35                  40                  45

Gln Glu Leu Thr Ala Ala Lys Lys His Gly Thr Lys Asn Lys Arg Ala
    50                  55                  60

Ala Leu Gln Ala Leu Lys Arg Lys Lys Arg Tyr Glu Lys Gln Leu Ala
65                  70                  75                  80

Gln Ile Asp Gly Thr Leu Ser Thr Ile Glu Phe Gln Arg Glu Ala Leu
                85                  90                  95

Glu Asn Ala Asn Thr Asn Thr Glu Val Leu Lys Asn Met Gly Tyr Ala
            100                 105                 110

Ala Lys Ala Met Lys Ala Ala His Asp Asn Met Asp Ile Asp Lys Val
        115                 120                 125

Asp Glu Leu Met Gln Asp Ile Ala Asp Gln Gln Glu Leu Ala Glu Glu
    130                 135                 140

Ile Ser Thr Ala Ile Ser Lys Pro Val Gly Phe Gly Glu Glu Phe Asp
145                 150                 155                 160

Glu Asp Glu Leu Met Ala Glu Leu Glu Glu Leu Glu Gln Glu Glu Leu
                165                 170                 175

Asp Lys Asn Leu Leu Glu Ile Ser Gly Pro Glu Thr Val Pro Leu Pro
            180                 185                 190

Asn Val Pro Ser Ile Ala Leu Pro Ser Lys Pro Ala Lys Lys Lys Glu
        195                 200                 205

Glu Glu Asp Asp Asp Met Lys Glu Leu Glu Asn Trp Ala Gly Ser Met
    210                 215                 220
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<210> 55

<211> 675

<212> DNA

<213> Mus musculus

<400> 55

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acccccccagg aggccatcca gcggcttcgg gacacggagg agatgttaag caagaagcag 120

gagttcctgg agaagaaaat cgaacaggag ctgacggctg ccaagaagca cggcaccaaa 180

aataagcgcg ccgccctgca ggctctgaag cgcaagaaga ggtatgagaa gcagctggca 240

caaattgatg gcaccctgtc aaccatcgag ttccagcggg aggccctaga gaacgccaac 300

accaacacgg aggtgctcaa gaacatgggc tatgccgcca aggccatgaa ggctgcccac 360

gacaacatgg acattgataa ggtggatgag ttaatgcagg acattgctga ccagcaagaa 420

cttgcagagg agatttccac agctatctcc aaacctgtgg gctttggaga agagttcgac 480

gaggatgagc tcatggcaga gttggaggaa cttgaacaag aggagttgga caagaatttg 540

ttggagatca gtgggcccga aacagtccct ctaccaaatg tcccctccgt agccctacca 600

tccaaacccg ccaagaagaa ggaagaggaa gatgacgaca tgaaggaatt ggagaactgg 660

gccggatcca tgtaa 675

<210> 56

<211> 224

<212> PRT

<213> Mus musculus

<400> 56

Met Ser Val Phe Gly Lys Leu Phe Gly Ala Gly Gly Gly Lys Ala Gly
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Lys Gly Gly Pro Thr Pro Gln Glu Ala Ile Gln Arg Leu Arg Asp Thr
20 25 30

Glu Glu Met Leu Ser Lys Lys Gln Glu Phe Leu Glu Lys Lys Ile Glu
35 40 45

Gln Glu Leu Thr Ala Ala Lys Lys His Gly Thr Lys Asn Lys Arg Ala
50 55 60

Ala Leu Gln Ala Leu Lys Arg Lys Lys Arg Tyr Glu Lys Gln Leu Ala
65 70 75 80

Gln Ile Asp Gly Thr Leu Ser Thr Ile Glu Phe Gln Arg Glu Ala Leu
85 90 95

Glu Asn Ala Asn Thr Asn Thr Glu Val Leu Lys Asn Met Gly Tyr Ala

100 105 110

Ala Lys Ala Met Lys Ala Ala His Asp Asn Met Asp Ile Asp Lys Val
115 120 125

Asp Glu Leu Met Gln Asp Ile Ala Asp Gln Gln Glu Leu Ala Glu Glu
130 135 140

Ile Ser Thr Ala Ile Ser Lys Pro Val Gly Phe Gly Glu Glu Phe Asp
145 150 155 160

Glu Asp Glu Leu Met Ala Glu Leu Glu Glu Leu Glu Gln Glu Glu Leu
165 170 175

Asp Lys Asn Leu Leu Glu Ile Ser Gly Pro Glu Thr Val Pro Leu Pro
180 185 190

Asn Val Pro Ser Val Ala Leu Pro Ser Lys Pro Ala Lys Lys Lys Glu
195 200 205

Glu Glu Asp Asp Asp Met Lys Glu Leu Glu Asn Trp Ala Gly Ser Met
210 215 220

<210> 57

<211> 1524

<212> DNA

<213> Drosophila melanogaster

<400> 57
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ccgccgcctc atgactacag cagctatcgc tggttcatcc tggagcccgc agtttttta 180
atcttcttcg ccagaaattt aattggggcg gtttatcaga accaaattct ctaccaaacc 240
tgcatcacca tcgagaaatt caatgccacg caatgtgaac cgctgctggg cattgatcgc 300
ggatcggacg cggataaaga agtcgaggtg atagtacaga cgtattctgc aaatattatg 360
atgacaacct ctctgctaga gagcattatt cctgccttcg cgagtctgtt cctgggtccc 420
tggtccgaca agttcggaag gcggccaatc ctgctgacaa cttttacggg ctacctcact 480
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tggttcctcc tttcctcggt tccttccgtc gtaagcggcg gaacttgcgc cttgattact 600
ggaatctatt gctacatatc cgatgtggcc aaggagcgaa agaaggctct gagaatggtc 660
ctcaatgaag cctccctctg tgctggcata atggtgggca atgtggccag cggttatatc 720
tatgctgcca caaatgctct ggtgttgttt tccattgctg gtagcctgat gatgtttgcc 780
ttgatgtacg tgcttctgtt tgtacctgaa agcctaaatc caggtgacat tcacaccgga 840

tcgcgagtcc gtgagttctt ccgtttcgat ttggtcacgg acctgattcg cacctgcttt 900
aagaggcgcc ccaactttga tcgcacaatc atctggctta caatgattgc ccttacgata 960
gccattttcg acatggaggg agagagcact gtaaattaca tgttcgtgca ggataaattc 1020
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ggcagcatcg ttggcatgtt ggtattgcgc cgcgttctaa agatgtctat cgtaaccatg 1140
gcaatgctct ccctggcttg ctgtgttctg gagagcacgg ttcgagccac agcagtctac 1200
tggcaagagc tgtatctggg catgacgctg ggtatgatgc gtggcgtcat gggacctatg 1260
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aaggcaactt tggaaaatta tcccggagct ttcaacttta ttagcgccgc tctctacttt 1440
gtgtgttaca ttctgatagc cgtgatcttc ggcatccaga agtcgatggg tagtagcagt 1500
gtctaccagg ccattggcag ctaa 1524

<210> 58

<211> 220

<212> PRT

<213> Drosophila melanogaster

<400> 58

Met Phe Gly Gly Lys Lys Glu Val Ala Pro Thr Thr Gly Glu Ala Ile
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Gln Lys Leu Arg Glu Thr Glu Asn Met Leu Ile Lys Lys Gln Glu Phe
20 25 30

Leu Glu Ala Lys Ile Glu Asp Glu Leu Asn Ile Ala Arg Lys Asn Ala
35 40 45

Ser Lys Asn Lys Arg Val Ala Leu Gln Ala Leu Lys Lys Lys Lys Arg
50 55 60

Leu Glu Lys Gln Leu Gln Gln Ile Asp Gly Thr Leu Ser Thr Ile Glu
65 70 75 80

Met Gln Arg Glu Ala Leu Glu Ser Ala Asn Thr Asn Thr Ala Val Leu
85 90 95

Thr Thr Met Lys Asn Ala Ala Asp Ala Leu Lys Arg Ala His Gln Asn
100 105 110

Met Asp Val Asp Lys Val His Asp Met Met Asp Asp Ile Ala Glu Gln
115 120 125

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

Phe Gly Ala Asp Leu Asp Asp Glu Asp Leu Glu Arg Glu Leu Asp Glu
145 150 155 160

Leu Glu Gln Glu Asn Phe Asp Lys Glu Ile Ile Gly Ile Pro Glu Pro
165 170 175

Thr Pro Thr Leu Pro Glu Ala Pro Thr Glu Asp Leu Pro Glu Lys Ala
180 185 190

Lys Glu Lys Lys Lys Ala Thr Thr Thr Thr Ala Val Glu Asp Asp Asp
195 200 205

Asp Pro Asp Met Lys Gln Leu Leu Ser Trp Ser Asn
210 215 220

<210> 59

<211> 723

<212> DNA

<213> Saccharomyces cerevisiae

<400> 59
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cgtactcaaa ttacaaatca agagaatgaa gctagaatct ttttgacgaa gggcaataaa 180

gtaatggcga agaatgcact taaaaagaag aagacaatcg aacaactttt aagtaaggta 240

gaaggcacaa tggagtctat ggaacagcag ctattctcta tagaaagtgc aaacttaaat 300

ctagagacaa tgagggctat gcaggaaggt gctaaggcaa tgaaaactat tcacagtggc 360

cttgacatag ataaagtgga tgaaactatg gacgagataa gggagcaagt cgaattagga 420

gatgaaataa gcgacgctat atccaggcct ttaattactg gggcaaacga ggtggatgaa 480

gatgagctgg acgaggaatt ggacatgctg gctcaagaaa atgctaacca agaaacgtcc 540

aagatcgtta ataataatgt taatgcggcg cctatctcag agaacaaagt ctcactacct 600

agtgttccaa gtaataaaat taaacaaagt gagaactctg tgaaggacgg ggaagaggaa 660

gaggatgaag aagatgaaga tgaaaaagca ttaagagaac tacaagcaga aatggggctt 720

tga 723

<210> 60

<211> 240

<212> PRT

<213> Saccharomyces cerevisiae

<400> 60

Met Trp Ser Ser Leu Phe Gly Trp Thr Ser Ser Asn Ala Lys Asn Lys
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Glu Ser Pro Thr Lys Ala Ile Val Arg Leu Arg Glu His Ile Asn Leu
20 25 30

Leu Ser Lys Lys Gln Ser His Leu Arg Thr Gln Ile Thr Asn Gln Glu
35 40 45

Asn Glu Ala Arg Ile Phe Leu Thr Lys Gly Asn Lys Val Met Ala Lys
50 55 60

Asn Ala Leu Lys Lys Lys Lys Thr Ile Glu Gln Leu Leu Ser Lys Val
65 70 75 80

Glu Gly Thr Met Glu Ser Met Glu Gln Gln Leu Phe Ser Ile Glu Ser
85 90 95

Ala Asn Leu Asn Leu Glu Thr Met Arg Ala Met Gln Glu Gly Ala Lys
100 105 110

Ala Met Lys Thr Ile His Ser Gly Leu Asp Ile Asp Lys Val Asp Glu
115 120 125

Thr Met Asp Glu Ile Arg Glu Gln Val Glu Leu Gly Asp Glu Ile Ser
130 135 140

Asp Ala Ile Ser Arg Pro Leu Ile Thr Gly Ala Asn Glu Val Asp Glu
145 150 155 160

Asp Glu Leu Asp Glu Glu Leu Asp Met Leu Ala Gln Glu Asn Ala Asn
165 170 175

Gln Glu Thr Ser Lys Ile Val Asn Asn Asn Val Asn Ala Ala Pro Ile
180 185 190

Ser Glu Asn Lys Val Ser Leu Pro Ser Val Pro Ser Asn Lys Ile Lys
195 200 205

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

Asp Glu Asp Glu Lys Ala Leu Arg Glu Leu Gln Ala Glu Met Gly Leu
225 230 235 240