
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
5 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
10 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*
15 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)
20 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
25 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
30 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 phosphodiester, 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.

5 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.

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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
15 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:

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| 20 | SEQ ID NO. 1 | the nucleotide sequence of the <i>C. elegans</i> gene C13F10.2 (Wormbase accession No. CE08144) |
| | SEQ ID NO. 2 | the deduced amino acid sequence of the <i>C. elegans</i> 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) |
| 25 | 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 <i>Drosophila</i> homolog of C13F10.2 (GenBank accession No. AE003541) |
| 30 | SEQ ID NO. 6 | the deduced amino acid sequence of the <i>Drosophila</i> 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)
- 5 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)
- 10 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)
- 15 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)
- 20 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)
- 25 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)
- 30 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)
- 5 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
10 (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)
- 15 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)
- 20 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
25 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)
- 30 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)
- 5 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)
- 10 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
15 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)
- 20 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
25 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
30 (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)
- 5 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)
- 10 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)
- 15 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)

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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).

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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.

- 10 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.
- 15 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
- 20 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.
- 25 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
- 30 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.

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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).

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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).

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C. elegans gene	e-value for the alignment with the C. elegans gene on amino acid level
C13F10.2	Human orthol. $6 \cdot 10^{-13}$ Drosoph. orthol. $1 \cdot 10^{-19}$
C25A1.9	Human orthol. $8 \cdot 10^{-6}$
F54B3.3	Human orthol. $1 \cdot 10^{-170}$ Mouse homol. $3 \cdot 10^{-15}$ Rat homol. $8 \cdot 10^{-15}$ Drosoph. orthol. $1 \cdot 10^{-163}$ Yeast homol. $8 \cdot 10^{-15}$
F08B6.2	Human orthol. $4 \cdot 10^{-6}$ Rat homol. $2 \cdot 10^{-6}$ Drosoph. orthol. $2 \cdot 10^{-11}$
CD4.4	Human orthol. $1 \cdot 10^{-9}$ (GenBank Acc.No. NP_078943) Human orthol. $2 \cdot 10^{-5}$ (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.

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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.

10 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
15 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
20 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), ³²P-dCTP-labeled (specific activity > 1 x 10⁹ 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 synthesized 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
5 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
10 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.

15 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
20 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
25 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
30 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.

5 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.

10 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
15 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
20 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-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.

25

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.

30 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), pcDNA1 (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
5 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
10 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.

15

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
20 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
25 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,
30 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.

- 5 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:

- 10 (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),

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

- 20 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
25 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

30

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.

- 5 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
10 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
15 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
20 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
25 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
30 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
5 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,
10 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
15 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,
20 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
25 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
30 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
5 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
10 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).

15 "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 restenosis, or a neoplastic disease, the latter preferably selected from the group consisting of lymphoma, lung cancer, colon cancer,
20 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,
25 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,
30 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:

- 5 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
10 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),
15 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
20 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:

- 25 (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),

30

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.

5

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.

10

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.

15 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
20 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
25 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,
- 5 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
10 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
15 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,
20 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.

25

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
30 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
5 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
10 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
15 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.

20

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.

25

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
30 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.

5

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
10 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.

15 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.

20 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)

25

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 analysis 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
30 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 thyroxine, 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 activating 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
5 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,
10 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.
15 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.

20 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
25 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.

30 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.

15

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.

25
30

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 polypeptide at the solid phase, and

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

5 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 baculovirus-based expression in insect cells.

Step b) comprises the isolation and optionally the subsequent purification of said
10 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
15 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
20 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 occurring homologs, preferably orthologs, more preferably human orthologs, but also derivatives of these polypeptides, in particular fusion proteins or polypeptides comprising a tag-sequence.

25

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
30 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.

- 5 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.
- 10 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.

- 15 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.

- 20 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.

- 25 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
5 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
10 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.
15 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.
20

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

25 **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.
- 30 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 *Drosophila* 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.

5

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
10 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
15 "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 μ l, with Taq polymerase using 0.8 μ M primers and approximately 0.1 μ g of wild-type (N2 strain) genomic DNA template. The
20 PCR products were EtOH precipitated, washed with 70% EtOH and resuspended in 7.0 μ l TE. 1.0 μ l of the PCR reaction was pipetted into each of two fresh tubes for 5 μ l 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 μ l with RNase-free water and then combined.
25 The mixed RNA was purified using RNeasy kits according to the manufacturer's instructions (Qiagen), and eluted into a total of 130 μ l of RNase-free H₂O. 50 μ l of this was mixed with 10 μ l 6X injection buffer (40 mM KPO₄ 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
30 μ g/ μ l. 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

5 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
10 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
15 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
20 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
25 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
30 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
 5 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
 10 "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,
 15 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
 20 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
 25 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
 30 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

- 48 -

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 fertilization, 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 fertilization, 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.

10 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 fertilization, while the female pronucleus is completing its meiotic divisions, until the 2 cell stage, ~15 to 20 minutes later.

25 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: "TAATACGACTCACTATAGGAACCTTTTCAGGTCCGCTCAA" 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 fertilization, 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 fertilization, while the female pronucleus is completing its meiotic divisions, until the 4 cell stage, ~30 minutes later.

- 54 -

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: "TAATACGACTCACTATAGGTTCTGGGAAACAGAGGAGATG" with

- 55 -

"AATTAACCCTCACTAAAGGCCTTGTCAGCTTCTTTTCGCT" 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
5 differential interference contrast (DIC) microscopy. Embryo recordings started ~20 minutes after fertilization, 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
10 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
15 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
20 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
25 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

30 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

- 56 -

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

The following siRNA sequences were used:

5	scrambled negative control	5-AGUACUGCUUACGAUACGGTT-3 3-TTUCAUGACGAAUGCUAUGCC-5
10	positive control (PCNA, proliferating cell nuclear antigen)	5-GGAGAAAGUUUCAGACUAUTT-3 3-GTCCUCUUUCAAGUCUGAUA-5
	NP_056972.1	5-GGUUGCUCACGCUUAUUUUTT-3 3-CTCCAACGAGGUCGAAUAAAA-5
15	CAD38936	5-GGUUCUCUUUGAAGCCUAUTT-3 3-GTCCAAGAGAAACUUCGGAUA-5
	NP_060387.1	5-GGCUUCAGGGAAAAUACUGTT-3 3-TTCCGAAGUCCCUUUUAUGAC-5
20	NP_076974.1	5-GGACCCUAGUAGAGAUGAATT-3 3-CTCCUGGGAUCAUCUCUACUU-5
25	NP_060658.1	5-GUCCACAGGUGCCUCAUUTT-3 3-TTCAGGGUGUCCACGGAGUAA-5

Transfection

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

30 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 (Invitex 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 apoptosis 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

- 59 -

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.

SEQUENCE LISTING

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 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

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
 420 425 430

Tyr Glu Asn Arg Glu Ala Leu Val Ala Asn Asp Ser Glu Asn Ser Ala
 435 440 445

Asp Leu Asp Asp Thr
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<210> 11

<211> 1833

<212> DNA

<213> *Caenorhabditis elegans*

<400> 11

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tccttcgact caacagcttt ggagcgtgcc gccaaaggctg ctctgtgatct agagaaattt	240
ccaaatgcc aagaagctct tgaattgtcg agaattgcaag aagttacacg ccaaaaagag	300
gtcgagaacg agaccaagaa gatcgaagct caattggcca atatgaaatc agagcacatt	360
cgtgttgctg aagaagaacg gaggaagact ttgggagaag agactaaaca tgcgcattcg	420
cgtgctgaat atcaagatca attggccaga aagagagccg aagaggagct tgccatgaaa	480
gctagaatgc aggaagaaag cctccgaaaa caagaagagt ctgtcaagaa gcaggaacaa	540
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gctgcagtag gaggattgac tgctttggct gtcggctggt ataccgctaa acgaggaact	840
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cgtcagaaga aggatccact gaatggagtt gtattaccac ctgcttttga acgtcgtctt	1020

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<210> 12

<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
 100 105 110

Ala Asn Met Lys Ser Glu His Ile Arg Val Ala Glu Glu Glu Arg Arg
 115 120 125
 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

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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 595 600 605
 Ala Val
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<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 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

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

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
 545 550 555 560

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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<210> 15

<211> 2421

<212> DNA

<213> Mus musculus

<400> 15

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<210> 16

<211> 806

<212> PRT

<213> Mus musculus

<400> 16

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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
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 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 ₃₅₅ Ala Leu Arg Arg Phe ₃₆₀ Gly Arg Phe Asp Arg ₃₆₅ Glu Val Asp		
Ile Gly ₃₇₀ Ile Pro Asp Ala Thr ₃₇₅ Gly Arg Leu Glu Ile ₃₈₀ Leu Gln Ile His		
Thr ₃₈₅ Lys Asn Met Lys Leu ₃₉₀ Ala Asp Asp Val Asp ₃₉₅ Leu Glu Gln Val Ala ₄₀₀		
Asn Glu Thr His Gly ₄₀₅ His Val Gly Ala Asp ₄₁₀ Leu Ala Ala Leu Cys ₄₁₅ Ser		
Glu Ala Ala Leu ₄₂₀ Gln Ala Ile Arg Lys ₄₂₅ Lys Met Asp Leu Ile ₄₃₀ Asp Leu		
Glu Asp Glu ₄₃₅ Thr Ile Asp Ala Glu ₄₄₀ Val Met Asn Ser Leu ₄₄₅ Ala Val Thr		
Met Asp ₄₅₀ Asp Phe Arg Trp Ala ₄₅₅ Leu Ser Gln Ser Asn ₄₆₀ Pro Ser Ala Leu		
Arg Glu Thr Val Val Glu ₄₇₀ Val Pro Gln Val Thr ₄₇₅ Trp Glu Asp Ile Gly ₄₈₀		
Gly Leu Glu Asp Val ₄₈₅ Lys Arg Glu Leu Gln Glu Leu Val Gln Tyr ₄₉₅ Pro		
Val Glu His Pro ₅₀₀ Asp Lys Phe Leu Lys ₅₀₅ Phe Gly Met Thr Pro ₅₁₀ Ser Lys		
Gly Val Leu ₅₁₅ Phe Tyr Gly Pro Pro Glu Cys Gly Lys Thr ₅₂₅ Leu Leu Ala		
Lys Ala ₅₃₀ Ile Ala Asn Glu Cys ₅₃₅ Gln Ala Asn Phe Ile ₅₄₀ Ser Ile Lys Gly		
Pro Glu Leu Leu Thr Met ₅₅₀ Trp Phe Gly Glu Ser ₅₅₅ Glu Ala Asn Val Arg ₅₆₀		
Glu Ile Phe Asp Lys ₅₆₅ Ala Arg Gln Ala Ala Pro Cys Val Leu Phe ₅₇₅ Phe		
Asp Glu Leu Asp ₅₈₀ Ser Ile Ala Lys Ala ₅₈₅ Arg Gly Gly Asn Ile ₅₉₀ Gly Asp		
Gly Gly Gly ₅₉₅ Ala Ala Asp Arg Val Ile Asn Gln Ile Leu Thr Glu Met		
Asp Gly ₆₁₀ Met Ser Thr Lys Lys ₆₁₅ Asn Val Phe Ile Ile ₆₂₀ Gly Ala Thr Asn		

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
785 790 795 800

Asp Asp Asp Leu Tyr Gly
805

<210> 17

<211> 2870

<212> DNA

<213> Rattus norvegicus

<400> 17

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ctaccattct cgtagccgtt accctcaggc cgccacagcc gccgaccggg agaggcgcg	240

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<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
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Arg Glu Ala Val Cys Ile Val Leu Ser Asp Asp Thr Cys Ser Asp Glu
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Lys Ile Arg Met Asn Arg Val Val Arg Asn Asn Leu Arg Val Arg Leu
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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
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 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
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 Cys Arg Lys Gln Leu Ala Gln Ile Lys Glu Met Val Glu Leu Pro Leu
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 Arg His Pro Ala Leu Phe Lys Ala Ile Gly Val Lys Pro Pro Arg Gly
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 Ile Leu Leu Tyr Gly Pro Pro Gly Thr Gly Lys Thr Leu Ile Ala Arg
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 Ala Val Ala Asn Glu Thr Gly Ala Phe Phe Phe Leu Ile Asn Gly Pro
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 Glu Ile Met Ser Lys Leu Ala Gly Glu Ser Glu Ser Asn Leu Arg Lys
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 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
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 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
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Glu Asp Glu Thr Ile Asp Ala Glu Val Met Asn Ser Leu Ala Val Thr
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Met Asp Asp Phe Arg Trp Ala Leu Ser Gln Ser Asn Pro Ser Ala Leu
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Arg Glu Thr Val Val Glu Val Pro Gln Val Thr Trp Glu Asp Ile Gly
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Gly Leu Glu Asp Val Lys Arg Glu Leu Gln Glu Leu Val Gln Tyr Pro
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Val Glu His Pro Asp Lys Phe Leu Lys Phe Gly Met Thr Pro Ser Lys
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Gly Val Leu Phe Tyr Gly Pro Pro Gly Cys Gly Lys Thr Leu Leu Ala
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Pro Glu Leu Leu Thr Met Trp Phe Gly Glu Ser Glu Ala Asn Val Arg
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Glu Ile Phe Asp Lys Ala Arg Gln Ala Ala Pro Cys Val Leu Phe Phe
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Asp Glu Leu Asp Ser Ile Ala Lys Ala Arg Gly Gly Asn Ile Gly Asp
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 595 600 605

Asp Gly Met Ser Thr Lys Lys Asn Val Phe Ile Ile Gly Ala Thr Asn
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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
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Glu Phe Leu Ala Lys Met Thr Asn Gly Phe Ser Gly Ala Asp Leu Thr
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Glu Ile Cys Gln Arg Ala Cys Lys Leu Ala Ile Arg Glu Ser Ile Glu
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Ser Glu Ile Arg Arg Glu Arg Glu Arg Gln Thr Asn Pro Ser Ala Met
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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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Asp Asp Asp Leu Tyr Gly
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<210> 19

<211> 2751

<212> DNA

<213> *Drosophila melanogaster*

<400> 19

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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
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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
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Asn Pro Leu His Tyr Leu Lys Arg Leu Arg Ala Lys Pro Thr Asp Ala
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Leu Gln Gly Val Val Leu Asn Pro Lys Leu Glu Glu Arg Leu Arg Asp
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Ile Ala Ile Ala Thr Lys Asn Thr Arg Ile Asn Lys Gly Met Tyr Arg
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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
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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
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Gln Asn Pro Lys Phe Met Leu Val Leu Ala Ser Asn Thr Pro Glu Gln
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Phe Asp Tyr Ala Ile Asn Asp Arg Leu Asp Glu Met Val Glu Phe Thr
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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
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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
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Ala Ala Val Tyr Ala Ser Glu Asp Gly Leu Leu Thr Glu Lys Met Val
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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
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Gln Leu Pro His Pro Ser Pro
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<210> 21

<211> 2244

<212> DNA

<213> *Saccharomyces cerevisiae*

<400> 21

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<210> 22

<211> 747

<212> PRT

<213> *Saccharomyces cerevisiae*

<400> 22

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

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

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

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

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Ala	Arg	Ala	Glu	Leu	Glu	Glu	Ile	Val	Asp	Phe	Leu	Lys	Asp	Pro	Thr
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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
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cgtactccga tcaactgtttc 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
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 gccttccagc gggagatggc gtccaagacc atccccgagc tgctgaagtg gatcgaggac 120
 gggatcccca aggaccctt 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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 ttgcagggat tggactcaga gaaacagacc cagggcatgg agacagggtg tgcctaggag 120
 gaggaggcgg tcctgagggg ctgcacccca ggggaggggg cggggctggg aatgggatct 180
 gcagaaccgc cagccatccc agccctgagc tgcaacagcc atgtccaaca acatggccaa 240
 gatcgctgag gcccgcaaga cgggtggagca actgaagctg gaggtgaaca tcgatcgcat 300
 gaagggtgtcg caggcggcag cggagctatt ggctttctgc gaaacgcacg ctaaggatga 360
 cccactgggtg actcctgtcc ctgccgccga gaatcccttc cgcgacaaac gactcttttg 420
 caccctgtct tgagccccc aagatagtttt atcctccgc gcagaaatat gaatccaata 480
 aacttggtga cttggtggtg cctgccattt aggggaaaat gaggcacggg gcaaaaacgt 540
 gggggccacc ttgtgggga 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
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 tcgttcacatc aggagaacga gaaaaatgat ccgttgatca atgcgccgga taagaagaac 180
 aatccatggg ccgaaaaggg caaatgccct caacatcatc agcaattaga tacccttagc 240
 caatgtagca gccaaagtttt ggggcaggat ttgggtgaat ccccgatct ggtgccggtg 300
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 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

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gaatcgatta ttgtcaatct cccgcagggtc cgtcfaatgc cgactgataa ggaatcagct      180
cttgccgcaa ataaatcatt agcagaatgg aatttagctc aaaagccgag aatcgatgct      240
gccaaaacgc aaacgggttga 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 ctgcgagcac ttcttcgtga acaaacgtat      540
tcttcatatg ctcaaccaac tgtacctcct ccaatgccac acgctcagcc tggataccca      600
acaggaaatc acatgcctgg aataggaaat attcaattcg gatctggcta ttcaggatat      660
ccaaatattt ctcaaccttc tgctgggtcgt catccatttt tctga                        705

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<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
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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

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 ctgctggagg acgagggccca gctgacggag atggtgcaga agatggagga gacacagaat 120
 gttagctta acaaagaaat gacacttgcc agcaaccgga gcctggcaga aggaaacctt 180

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ttgtaccagc cccagctgga cacgttgaaa gcacgcttga cccagaaata ccaggaactc 240
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gcttccttgg agaccctgtt agcacttctt caggcagaag gggccaagat tgaggaagac 360
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gtctatcaga gcaaacggaa actggcccac atgcgacggg tgaaaatcga gaagctccag 480
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cccgaaactgg cacctaccgc ccccttccc taccctgccc cagaggccag tgggcctcct 600
gccgttgac ctcggcgcat cccccccca ccaccccggt tgcttgctgg acgcttagcc 660
accccgttta ctgcggccat gagttcggga caggccgtgc cgtaccagc attacagtgc 720
ccgcccctgc ccccccgctt gggcctcccc actcagcaag gattctcttc gcagttcgtg 780
tccccatata cgccacctct cctcagaga cccccgccc ggctccctcc acaccagccg 840
ggtttcatcc tccagtga 858

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<210> 34

<211> 285

<212> PRT

<213> Homo sapiens

<400> 34

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

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```

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

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```

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

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```

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

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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

<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
 tggagcgggtg ccaggagcag aaggcaaagc tggagaaatt ttcttcagca ctgcagccag 360
 ggaccttggt agaccttctg caggtggaag gcatgaagat cgaagaagag tccgaggcca 420
 tggctgagaa gttcctggag ggcgaggtgc ccctggaaac gttcctggag aatttttctt 480
 ccatgaggat gctgtccac ctgcgccggg ttgcgtgga aaagctccag gaagtggatga 540

ggaagccag ggcttcccag gagctggccg gcgatgcccc tccaccccg tccacacccc 600
 cgggtgcgccc agacccccag ggaacacccc ctgtggttga agagcagccg cagccaccat 660
 tagccatgcc tccctaccct ttgccctaca gcccatcccc cagcctgcct gtggggcccca 720
 ctgcccagtg agccctgcca ccggccccc tcccagtagt gtcccagccc tccctctaca 780
 gcggggcctct gggcccccact taccggcag cccagcttgg acccaggggt gctgcgggtt 840
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 gtgcctctgg gcctgggtac ccttgccggg gaggcagggc cccagtcct gggtatcctc 960
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 ccagctttcc aggccagccc cagccctcag tgcccctgca gccccttat cccccgggc 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
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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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<210> 38

<211> 214

<212> PRT

<213> *Drosophila melanogaster*

<400> 38

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 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
180 185 190

Gly Gly Ser Ala Pro Tyr Pro Ile Met Gly Pro Leu Met Pro Met Pro
195 200 205

Pro Pro Ser Arg Pro Tyr
210

<210> 39

<211> 2319

<212> DNA

<213> Caenorhabditis elegans

<400> 39

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cataacgtag acaaaaattt cttcaccgac ggctggcttg aaacaatgcc cgagaacagg	300
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aatgctgata aaattctcgt tgacgcagag ctggaaattg aacgtttacg gactgaaaca	780
gagaatcaga ggaaagaaat tgaacggctg actaaatcct ttgaaactgc acaacacgat	840
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tttaaaggga tcgtttttga acttaccac gagaatgatg tgcttcgtag atcggacaaa	1020

gagagacaga gactacaaac agtgctggat gctgctcaat ccgatttaga tgaatggaaa 1080
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<210> 40

<211> 777

<212> PRT

<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

Asp Met Ala Val Trp Met Glu Gly Leu Asp Ala Thr Lys Leu Pro Leu
 50 55 60
 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
 165 170 175
 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

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
610 615 620

Thr Ala Leu Gln Lys Ala Lys Ala Val Ile Asp Glu Leu Glu Tyr Asn
625 630 635 640

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

Val Leu Gly Phe Leu Val Phe Ile Ala Trp Met Phe Ile Asn Ile Asn
755 760 765

Ser Ala Leu Asn Ala Pro Pro Asn Ala
770 775

<210> 41

<211> 2187

<212> DNA

<213> Homo sapiens

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gttgccatgg cacaagttct tcatcaaatt gatgcagctt gggttaacga atcttggtta 180
agccgaatta aagaggatgt tggggacaac tggagaataa aggccagtaa tgtaaagaag 240
gtccttcaag gaattatgag ttattatcat gagtttttgg ggcagcagat ttcagaagca 300
cttatccctg atttaaacca aataaccgaa tgttcagatc cagtggagct tgggaggttg 360

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agtaaagaaa tattgagctc tcttccaaat gatgctgttg gagaattgga gcaacagctt 540
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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

Leu Gln Glu Glu Asn Phe Arg Leu Glu Ala Ala Lys Asp Asp Tyr Arg
 260 265 270

Val His Cys Glu Glu Leu Glu Lys Gln Leu Ile Glu Phe Gln His Arg
 275 280 285

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
 500 505 510

Ser Lys Glu Arg Ile Arg Glu Leu Gln Gln Gln Ile Glu Asp Leu Gln
 515 520 525

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
645 650 655

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
690 695 700

Leu Ala Gln Gln Arg His Ile Thr Asn Thr Arg Arg Asn Leu Ser Val
705 710 715 720

Lys Val Pro Ala Thr Thr Ser Asp
725

<210> 43

<211> 4597

<212> DNA

<213> Rattus norvegicus

<400> 43
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aagctggacc ctggcagtgt cttatttaag aaactttaaa ttatgacgtt aagcctcata 4500
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<210> 44

<211> 1320

<212> PRT

<213> Rattus norvegicus

<400> 44

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Met Ser Met Leu Lys Pro Ser Gly Leu Lys Ala Pro Thr Lys Ile Leu
1      5      10     15

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Lys Pro Gly Ser Thr Ala Leu Lys Thr Pro Ala Ala Ala Ala Ala Pro
20     25     30

```

```

Leu Glu Lys Thr Val Pro Ser Glu Lys Ala Ser Gly Pro Pro Ser Ser
35     40     45

```

```

Glu Thr Gln Glu Glu Phe Val Asp Asp Phe Arg Val Gly Glu Arg Val
50     55     60

```

```

Trp Val Asn Gly Asn Lys Pro Gly Phe Ile Gln Phe Leu Gly Glu Thr
65     70     75     80

```

```

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

```

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Ala Ser Pro Leu Ser Thr Ala Ala Ala Thr Met Val Ser Ser Ser Pro
145    150    155    160

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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
195 200 205

Arg Glu Leu Lys Ile Gly Asp Arg Val Leu Val Gly Gly Thr Lys Ala
210 215 220

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

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
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<211> 1690

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<213> *Drosophila melanogaster*

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 Gly Ile Pro Gln Pro Ser Lys Met Lys Ala Pro Ser Ser Phe Gly Ser
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 Thr Gly Ser Val Ser Lys Ile Gly Arg Pro Cys Cys Asn His Thr Thr
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 Ser Asp Asp Asn Leu Ser Ser Ile Asn Ser Ala Tyr Thr Asp Asn Ser
 100 105 110
 Ser Ala Val Leu Thr Ala Asn Thr Glu Gln Phe Ile Ile Gly Gln Arg
 115 120 125
 Val Trp Leu Gly Gly Thr Arg Pro Gly Gln Ile Ala Phe Ile Gly Asp
 130 135 140
 Thr His Phe Ala Ala Gly Glu Trp Ala Gly Val Val Leu Asp Glu Pro
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 Asn Gly Lys Asn Asp Gly Cys Val Ser Gly Lys Arg Tyr Phe Gln Cys
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 Glu Pro Lys Arg Gly Ile Phe Ser Arg Leu Thr Arg Leu Thr Thr Tyr
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 Pro Leu Ala Gly Ala Gln Thr Pro Thr Ser Pro Leu Ala Lys Ser Ser
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 Pro Asp Arg Ser Arg Thr Val Ser Pro Thr Ala Ser Ile Arg Ser Ser
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 Met Leu Arg Ser Pro Gly Ile Gly Gly Lys Asn Gly Met Ala Val Gly
 225 230 235 240
 Asp Arg Val Ile Val Ser Ser Gly Phe Gly Ser Arg Pro Gly Ile Leu
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 Arg Tyr Leu Gly Glu Thr Gln Phe Ala Pro Gly Asn Trp Cys Gly Val
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Glu Leu Leu Lys Glu Glu Asn Glu Lys Gln Ala Gln Glu Ala Gln Ala
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Glu Phe Thr Arg Lys Leu Ala Glu Lys Ser Val Glu Val Leu Arg Leu
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595 600 605

Glu Arg Val Asn Lys Thr Asp Glu Cys Glu Ile Leu Gln Thr Glu Val
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Asp Met Leu Arg Leu Gln Lys Glu Gly Thr Glu Glu Lys Ser Thr Leu
660 665 670

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740 745 750

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755 760 765

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785 790 795 800

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Ser Gln Leu Lys Gln Ala Asn 1445 1450	Glu Glu Leu Gln Lys 1455	Ser Leu Gln
Gln Lys Gln Leu Leu Leu Glu 1460 1465	Lys Gly Asn Glu Phe 1470	Asp Thr Gln
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<212> DNA

<213> *Saccharomyces cerevisiae*

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<213> *Saccharomyces cerevisiae*

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Thr Arg Gly Trp Ile Ser Gln Gln Ser Arg Leu Gln Asn Gly Lys Tyr
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Pro Ser Pro Leu Val Met Lys Gln Glu Lys Glu Gln Val Asp Gln Phe
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Leu Met Ala Val Val Asn Asp Ser Pro His Val Gln Lys Leu Val Ala
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 Thr Lys His Gln Asn Ala Leu Leu Asp Ser Ser Val Leu Met Val Val
 325 330 335
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Thr Gly Leu Pro Lys Val Tyr Phe Ser Thr Tyr Phe Ile Gln Leu Phe
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 Gln Tyr Asn Glu Glu Ile Ser Gln Leu Asn Asp Glu Ile Thr Ser
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 Thr Gln Gln Glu Asn Glu Ser Ile Lys Lys Lys Asn Asp Glu Leu
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 Glu Gly Glu Val Lys Ala Met Lys Ser Thr Ser Glu Glu Gln Ser
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 Asn Leu Lys Lys Ser Glu Ile Asp Ala Leu Asn Leu Gln Ile Lys
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 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
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 1280 1285 1290
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 1295 1300 1305

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Arg	Lys	Leu	Leu	Asn	Glu	Gly	Ser	Ser	Thr	Ile	Thr	Gln	Glu	Tyr
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Ser	Glu	Lys	Ile	Asn	Thr	Leu	Glu	Asp	Glu	Leu	Ile	Arg	Leu	Gln
1385						1390					1395			
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1415						1420					1425			
Lys	Gln	Asn	Thr	Ile	Lys	Ser	Leu	Gln	Asp	Glu	Ile	Leu	Ser	Tyr
1430						1435					1440			
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1445						1450					1455			
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1460						1465					1470			
Ala	Ala	Gln	Glu	Ser	Lys	Ala	Lys	Val	Glu	Glu	Gly	Leu	Lys	Lys
1475						1480					1485			
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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			

Glu Lys Asp Ile Glu Glu Leu Lys Ser Lys Leu Arg Ile Glu Ala
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 1730 1735 1740
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 1745 1750 1755
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<211> 666

<212> DNA

<213> *Caenorhabditis elegans*

<400> 51

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atggctctcc agtgtttgaa tagaaagaga aatttcgaga agcagttggc ccatattgac      240
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agagctccac cagtcacgct tccggatact ccaaattattg cacttccagc agttccggct      600
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<210> 52

<211> 221

<212> PRT

<213> *Caenorhabditis elegans*

<400> 52

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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
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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

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Leu Lys Ala Ala His Asn Asn Met Asp Ile Asp Gln Val His Asp Leu
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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

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<210> 54

<211> 224

<212> PRT

<213> Homo sapiens

<400> 54

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 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
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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

<210> 55

<211> 675

<212> DNA

<213> Mus musculus

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<210> 56

<211> 224

<212> PRT

<213> Mus musculus

<400> 56

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 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
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<210> 57

<211> 1524

<212> DNA

<213> Drosophila melanogaster

<400> 57

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<211> 220

<212> PRT

<213> *Drosophila melanogaster*

<400> 58

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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
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<210> 59

<211> 723

<212> DNA

<213> *Saccharomyces cerevisiae*

<400> 59

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<210> 60

<211> 240

<212> PRT

<213> *Saccharomyces cerevisiae*

<400> 60

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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
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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

Claims

1. A method for the identification and characterization of drugs that inhibit or activate spindle formation or microtubule function during cell division, wherein the method comprises using a nucleic acid molecule in a screening assay for the identification of said drug, and performing a functional analysis for the spindle formation or microtubule function during cell division, wherein the nucleic acid molecule comprises
 - (a) a nucleic acid sequence encoding a polypeptide that exhibits a sequence identity of at least 70% over 100 residues on the amino acid level with the protein encoded by the nucleic acid sequence of SEQ ID NO: 3,
 - (b) a nucleic acid sequence that is antisense of the nucleic acid sequence as defined in (a), or
 - (c) a double-stranded RNA or a single-stranded RNA in the antisense or sense direction corresponding to the nucleic acid sequence as defined in (a).
2. The method of claim 1, wherein the nucleic acid molecule comprises
 - (a) the nucleic acid sequence of SEQ ID NO: 3,
 - (b) a nucleic acid sequence encoding a polypeptide that exhibits a sequence identity with the protein encoded by the nucleic acid sequence of SEQ ID NO: 3,
 - (c) a nucleic acid sequence that is antisense of the nucleic acid sequence as defined in (a) or (b), or
 - (d) a double-stranded RNA or a single-stranded RNA in the antisense or sense direction corresponding to the nucleic acid sequence as defined in (a) or (b).
3. The method of claim 1, further comprising
 - (a) transforming the nucleic acid molecule into a host cell or host organism,
 - (b) cultivating the host cell or host organism under conditions that allow the overexpression of the polypeptide encoded by, or RNA corresponding to, the nucleic acid

molecule either in the presence or in the absence of at least one candidate for an inhibitor- or activator-molecule, and

(c) analyzing the spindle formation or microtubule function during cell division in the cultivated cell or organism.