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(54) **NOUVEAUX AGONISTES DU RECEPTEUR FLT-3**

(54) **NOVEL FLT-3 RECEPTOR AGONISTS**

(57) Cette invention concerne de nouvelles protéines agonistes du récepteur flt-3, des ADN codant ces protéines agonistes du récepteur flt-3, des procédés de production de ces protéines, ainsi que des procédés d'utilisation de ces dernières.

(57) Disclosed are novel flt-3 receptor agonist proteins, DNAs which encode the flt-3 receptor agonist proteins, methods of making the flt-3 receptor agonist proteins and methods of using the flt-3 receptor agonist proteins.

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

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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | (43) International Publication Date: 7 May 1998 (07.05.98) |
| (21) International Application Number: PCT/US97/18700<br>(22) International Filing Date: 23 October 1997 (23.10.97)<br>(30) Priority Data:<br>60/030,094                      25 October 1996 (25.10.96)                      US<br>(71) Applicant (for all designated States except US): G.D. SEARLE & CO. [US/US]; Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US).<br>(72) Inventors; and<br>(75) Inventors/Applicants (for US only): MCWHERTER, Charles, A. [US/US]; 16564 Thunderhead Canyon Court, Wildwood, MO 63011 (US). FENG, Yiqing [US/US]; 423 Mission Court, St. Louis, MO 63130 (US). McKEARN, John, P. [US/US]; 18612 Babler Meadows Drive, St. Louis, MO 63038 (US). STATEN, Nicholas, R. [US/US]; 859 Queen Ann Place, St. Louis, MO 63122 (US). STREETER, Philip, R. [US/US]; 1555 Pond Road, Glencoe, MO 63038 (US). WOULFE, Susan, L. [US/US]; 1719 Woodmore Oaks Drive, Ballwin, MO 63021 (US). MINSTER, Nancy, I. [US/US]; 16080 Clarkson Woods, Chesterfield, MO 63017 (US). MINNERLY, John, C. [US/US]; 5824 Bristlecone Court, St. Louis, MO 63129 (US). |  | (74) Agent: G.D. SEARLE & CO.; P.O. Box 5110, Chicago, IL 60680-5110 (US).<br>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).<br><b>Published</b><br><i>With international search report.</i><br><i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> |                                                            |
| (54) Title: NOVEL flt-3 RECEPTOR AGONISTS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                            |
| (57) Abstract                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                            |
| Disclosed are novel flt-3 receptor agonist proteins, DNAs which encode the flt-3 receptor agonist proteins, methods of making the flt-3 receptor agonist proteins and methods of using the flt-3 receptor agonist proteins.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                            |

**NOVEL *flt3* RECEPTOR AGONISTS**

The present application claims priority under Title 35, United States Code, §119 of United States Provisional  
5 application Serial No. 60/030,094, filed October 25, 1996.

FIELD OF THE INVENTION

10 The present invention relates to human *flt3* receptor agonists. These *flt3* receptor agonists retain one or more activities of native *flt3* ligand and may also show improved hematopoietic cell-stimulating activity and/or an improved activity profile which may  
15 include reduction of undesirable biological activities associated with native *flt3* ligand and/or have improved physical properties which may include increased solubility, stability and refold efficiency.

BACKGROUND OF THE INVENTION

20 Colony stimulating factors which stimulate the differentiation and/or proliferation of bone marrow cells have generated much interest because of their therapeutic potential for restoring depressed levels of  
25 hematopoietic stem cell-derived cells. Colony stimulating factors in both human and murine systems have been identified and distinguished according to their activities. For example, granulocyte-CSF (G-CSF) and macrophage-CSF (M-CSF) stimulate the in vitro  
30 formation of neutrophilic granulocyte and macrophage colonies, respectively while GM-CSF and interleukin-3 (IL-3) have broader activities and stimulate the formation of both macrophage, neutrophilic and eosinophilic granulocyte colonies. Certain factors such  
35 as *flt3* ligand are able to predominately affect stem cells.

Tyrosine kinase receptors are growth factor receptors that regulate the proliferation and differentiation of a number of cell. Certain tyrosine kinase receptors function within the hematopoietic system. Flt3 ligand (Rosnet et al., *Oncogene*, **6**:1641-1650, 1991) and flk-2 (Matthews et al., *Cell*, **65**:1143-1152, 1991) are forms of a tyrosine kinase receptor that is related to c-fms and c-kit receptors. The flk-2 and flt3 receptors are similar in amino acid sequence and vary at two amino acid residues in the extracellular domain and diverge in a 31 amino acid segment located near the C-terminus.

flt3 ligand is a hematopoietic growth factor which has the property of being able to regulate the growth and differentiation of hematopoietic progenitor and stem cells. Because of its ability to support the growth and proliferation of progenitor cells, flt3 receptor agonists have potential for therapeutic use in treating hematopoietic disorders such as aplastic anemia and myelodysplastic syndromes. Additionally, flt3 receptor agonists will be useful in restoring hematopoietic cells to normal amounts in those cases where the number of cells has been reduced due to diseases or to therapeutic treatments such as radiation and chemotherapy.

WO 94/28391 discloses the native flt3 ligand protein sequence and a cDNA sequence encoding the flt3 ligand, methods of expressing flt3 ligand in a host cell transfected with the cDNA and methods of treating patients with a hematopoietic disorder using flt3 ligand.

US Patent No. 5,554,512 is directed to human flt3 ligand as an isolated protein, DNA encoding the flt3 ligand, host cells transfected with cDNAs encoding flt3

ligand and methods for treating patients with flt3 ligand.

WO 94/26891 provides mammalian flt3 ligands, including an isolate that has an insertion of 29 amino acids, and fragments thereof.

#### Rearrangement of Protein Sequences

In evolution, rearrangements of DNA sequences serve an important role in generating a diversity of protein structure and function. Gene duplication and exon shuffling provide an important mechanism to rapidly generate diversity and thereby provide organisms with a competitive advantage, especially since the basal mutation rate is low (Doolittle, *Protein Science* 1:191-200, 1992).

The development of recombinant DNA methods has made it possible to study the effects of sequence transposition on protein folding, structure and function. The approach used in creating new sequences resembles that of naturally occurring pairs of proteins that are related by linear reorganization of their amino acid sequences (Cunningham, et al., *Proc. Natl. Acad. Sci. U.S.A.* **76**:3218-3222, 1979; Teather & Erfle, *J. Bacteriol.* **172**: 3837-3841, 1990; Schimming et al., *Eur. J. Biochem.* **204**: 13-19, 1992; Yamiuchi and Minamikawa, *FEBS Lett.* **260**:127-130, 1991; MacGregor et al., *FEBS Lett.* **378**:263-266, 1996). The first in vitro application of this type of rearrangement to proteins was described by Goldenberg and Creighton (*J. Mol. Biol.* **165**:407-413, 1983). A new N-terminus is selected at an internal site (breakpoint) of the original sequence, the new sequence having the same order of amino acids as the original from the breakpoint until it reaches an amino acid that is at or near the original C-terminus. At this point the new sequence is joined, either directly or

through an additional portion of sequence (linker), to an amino acid that is at or near the original N-terminus, and the new sequence continues with the same sequence as the original until it reaches a point that  
 5 is at or near the amino acid that was N-terminal to the breakpoint site of the original sequence, this residue forming the new C-terminus of the chain.

This approach has been applied to proteins which range in size from 58 to 462 amino acids (Goldenberg &  
 10 Creighton, *J. Mol. Biol.* **165**:407-413, 1983; Li & Coffino, *Mol. Cell. Biol.* **13**:2377-2383, 1993). The proteins examined have represented a broad range of structural classes, including proteins that contain predominantly  $\alpha$ -helix (interleukin-4; Kreitman et al.,  
 15 *Cytokine* **7**:311-318, 1995),  $\beta$ -sheet (interleukin-1; Horlick et al., *Protein Eng.* **5**:427-431, 1992), or mixtures of the two (yeast phosphoribosyl anthranilate isomerase; Luger et al., *Science* **243**:206-210, 1989). Broad categories of protein function are represented in  
 20 these sequence reorganization studies:

### Enzymes

|    |                         |                                                                                                                                        |
|----|-------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| 25 | T4 lysozyme             | Zhang et al., <i>Biochemistry</i> <b>32</b> :12311-12318 (1993); Zhang et al., <i>Nature Struct. Biol.</i> <b>1</b> :434-438 (1995)    |
| 30 | dihydrofolate reductase | Buchwalder et al., <i>Biochemistry</i> <b>31</b> :1621-1630 (1994); Protasova et al., <i>Prot. Eng.</i> <b>7</b> :1373-1377 (1995)     |
| 35 | ribonuclease T1         | Mullins et al., <i>J. Am. Chem. Soc.</i> <b>116</b> :5529-5533 (1994); Garrett et al., <i>Protein Science</i> <b>5</b> :204-211 (1996) |

- Bacillus*  $\beta$ -glucanase Hahn et al., *Proc. Natl. Acad. Sci. U.S.A.* **91**:10417-10421 (1994)
- 5 aspartate Yang & Schachman, *Proc. Natl. Acad. Sci. U.S.A.* **90**:11980-11984 (1993)
- transcarbamoylase
- phosphoribosyl Luger et al., *Science* **243**:206-210  
anthranilate (1989); Luger et al., *Prot. Eng.*  
isomerase **3**:249-258 (1990)
- 10 pepsin/pepsinogen Lin et al., *Protein Science* **4**:159-166 (1995)
- glyceraldehyde-3- Vignais et al., *Protein Science*  
15 phosphate dehydro- **4**:994-1000 (1995)  
genase
- ornithine Li & Coffino, *Mol. Cell. Biol.*  
decarboxylase **13**:2377-2383 (1993)
- 20 yeast Ritco-Vonsovici et al., *Biochemistry*  
phosphoglycerate **34**:16543-16551 (1995)  
dehydrogenase
- 25 **Enzyme Inhibitor**
- basic pancreatic Goldenberg & Creighton, *J. Mol. Biol.* **165**:407-413 (1983)  
trypsin inhibitor
- 30 **Cytokines**
- interleukin-1 $\beta$  Horlick et al., *Protein Eng.* **5**:427-431 (1992)
- 35 interleukin-4 Kreitman et al., *Cytokine* **7**:311-318 (1995)

**Tyrosine Kinase  
Recognition Domain**

- 5     $\alpha$ -spectrin SH3 domain                      Viguera, et al., *J. Mol. Biol.* **247**:670-681 (1995)

**Transmembrane  
Protein**

- 10   omp A                                      Koebnik & Krämer, *J. Mol. Biol.* **250**:617-626 (1995)

**Chimeric Protein**

- 15   interleukin-4-*Pseudomonas* exotoxin fusion molecule                      Kreitman et al., *Proc. Natl. Acad. Sci. U.S.A.* **91**:6889-6893 (1994).

- 20            The results of these studies have been highly variable. In many cases substantially lower activity, solubility or thermodynamic stability were observed (*E. coli* dihydrofolate reductase, aspartate transcarbamoylase, phosphoribosyl anthranilate isomerase, glyceraldehyde-3-phosphate dehydrogenase, ornithine decarboxylase, omp A, yeast phosphoglycerate dehydrogenase). In other cases, the sequence rearranged protein appeared to have many nearly identical properties as its natural counterpart (basic pancreatic trypsin inhibitor, T4 lysozyme, ribonuclease T1, Bacillus  $\beta$ -glucanase, interleukin-1 $\beta$ ,  $\alpha$ -spectrin SH3 domain, pepsinogen, interleukin-4). In exceptional cases, an unexpected improvement over some properties of the natural sequence was observed, e.g., the solubility and refolding rate for rearranged  $\alpha$ -spectrin SH3 domain sequences, and the receptor affinity and anti-tumor activity of transposed interleukin-4-*Pseudomonas* exotoxin fusion molecule (Kreitman et al., *Proc. Natl.*
- 35

*Acad. Sci. U.S.A.* **91**:6889-6893, 1994; Kreitman et al., *Cancer Res.* **55**:3357-3363, 1995).

The primary motivation for these types of studies has been to study the role of short-range and long-range interactions in protein folding and stability. Sequence rearrangements of this type convert a subset of interactions that are long-range in the original sequence into short-range interactions in the new sequence, and vice versa. The fact that many of these sequence rearrangements are able to attain a conformation with at least some activity is persuasive evidence that protein folding occurs by multiple folding pathways (Viguera, et al., *J. Mol. Biol.* **247**:670-681, 1995). In the case of the SH3 domain of  $\alpha$ -spectrin, choosing new termini at locations that corresponded to  $\beta$ -hairpin turns resulted in proteins with slightly less stability, but which were nevertheless able to fold.

The positions of the internal breakpoints used in the studies cited here are found exclusively on the surface of proteins, and are distributed throughout the linear sequence without any obvious bias towards the ends or the middle (the variation in the relative distance from the original N-terminus to the breakpoint is ca. 10 to 80% of the total sequence length). The linkers connecting the original N- and C-termini in these studies have ranged from 0 to 9 residues. In one case (Yang & Schachman, *Proc. Natl. Acad. Sci. U.S.A.* **90**:11980-11984, 1993), a portion of sequence has been deleted from the original C-terminal segment, and the connection made from the truncated C-terminus to the original N-terminus. Flexible hydrophilic residues such as Gly and Ser are frequently used in the linkers. Viguera, et al. (*J. Mol. Biol.* **247**:670-681, 1995) compared joining the original N- and C-termini with 3- or 4-residue linkers; the 3-residue linker was less thermodynamically stable. Protasova et al. (*Protein Eng.* **7**:1373-1377, 1994) used 3- or 5-residue linkers in

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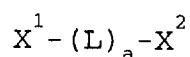
PCT/US97/18700

connecting the original N-termini of *E. coli*  
dihydrofolate reductase; only the 3-residue linker  
produced protein in good yield.

5

Summary of the Invention

The modified human flt3 receptor agonists of the  
 5 present invention can be represented by the Formula:



wherein;

- 10                   a is 0 or 1;  
                    $X^1$  is a peptide comprising an amino acid  
                   sequence corresponding to the sequence of residues n+1  
                   through J;  
                    $X^2$  is a peptide comprising an amino acid  
 15                  sequence corresponding to the sequence of residues 1  
                   through n;  
                   n is an integer ranging from 1 to J-1; and  
                   L is a linker.

20                  In the formula above the constituent amino acids  
                   residues of human flt3 ligand are numbered sequentially  
                   1 through J from the amino to the carboxyl terminus. A  
                   pair of adjacent amino acids within this protein may be  
                   numbered n and n+1 respectively where n is an integer  
 25                  ranging from 1 to J-1. The residue n+1 becomes the new  
                   N-terminus of the new flt3 receptor agonist and the  
                   residue n becomes the new C-terminus of the new flt3  
                   receptor agonist.

30                  The present invention relates to novel flt3  
                   receptor agonists of the following formula:

|    |                                                              |    |
|----|--------------------------------------------------------------|----|
|    | ThrGlnAspCysSerPheGlnHisSerProIleSerSerAspPheAlaValLysIleArg |    |
|    | 10                                                           | 20 |
| 35 | GluLeuSerAspTyrLeuLeuGlnAspTyrProValThrValAlaSerAsnLeuGlnAsp |    |
|    | 30                                                           | 40 |
| 40 | GluGluLeuCysGlyGlyLeuTrpArgLeuValLeuAlaGlnArgTrpMetGluArgLeu |    |
|    | 50                                                           | 60 |

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LysThrValAlaGlySerLysMetGlnGlyLeuLeuGluArgValAsnThrGluIleHis  
 70 80  
 5 PheValThrLysCysAlaPheGlnProProProSerCysLeuArgPheValGlnThrAsn  
 90 100  
 IleSerArgLeuLeuGlnGluThrSerGluGlnLeuValAlaLeuLysProTrpIleThr  
 110 120  
 10 ArgGlnAsnPheSerArgCysLeuGluLeuGlnCysGlnProAspSerSerThrLeuPro  
 130 140  
 ProProTrpSerProArgProLeuGluAlaThrAlaProThrAlaProGlnProProLeu  
 150 160  
 15 LeuLeuLeuLeuLeuLeuProValGlyLeuLeuLeuLeuAlaAlaAlaTrpCysLeuHis  
 170 180  
 TrpGlnArgThrArgArgArgThrProArgProGlyGluGlnValProProValProSer  
 20 190 200  
 ProGlnAspLeuLeuLeuValGluHis SEQ ID NO:145  
 209  
 25 wherein the N-terminus is joined to the C-terminus  
 directly or through a linker capable of joining the N-  
 terminus to the C-terminus and having new C- and N-  
 termini at amino acids;  
 30

|       |       |                   |
|-------|-------|-------------------|
| 28-29 | 42-43 | 93-94             |
| 29-30 | 64-65 | 94-95             |
| 30-31 | 65-66 | 95-96             |
| 31-32 | 66-67 | 96-97             |
| 32-33 | 86-87 | 97-98             |
| 34-35 | 87-88 | 98-99             |
| 36-37 | 88-89 | 99-100            |
| 37-38 | 89-90 | 100-101           |
| 38-39 | 90-91 | 101-102           |
| 39-40 | 91-92 | 102-103           |
| 40-41 | 92-93 | respectively; and |
| 41-42 |       |                   |

additionally said flt3 receptor agonist polypeptide can  
 be immediately preceded by (methionine<sup>-1</sup>), (alanine<sup>-1</sup>) or  
 (methionine<sup>-2</sup>, alanine<sup>-1</sup>).  
 35

A preferred embodiment is human flt3 receptor  
 agonist polypeptide, comprising a modified flt3 ligand  
 amino acid sequence of the Formula:

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```

      ThrGlnAspCysSerPheGlnHisSerProIleSerSerAspPheAlaValLysIleArg
                                10                                20
5   GluLeuSerAspTyrLeuLeuGlnAspTyrProValThrValAlaSerAsnLeuGlnAsp
                                30                                40
      GluGluLeuCysGlyGlyLeuTrpArgLeuValLeuAlaGlnArgTrpMetGluArgLeu
                                50                                60
10  LysThrValAlaGlySerLysMetGlnGlyLeuLeuGluArgValAsnThrGluIleHis
                                70                                80
      PheValThrLysCysAlaPheGlnProProProSerCysLeuArgPheValGlnThrAsn
15                                 90                                100
      IleSerArgLeuLeuGlnGluThrSerGluGlnLeuValAlaLeuLysProTrpIleThr
                                110                               120
20  ArgGlnAsnPheSerArgCysLeuGluLeuGlnCysGlnProAspSerSerThrLeu
                                130                               SEQ ID NO:144

```

wherein the N-terminus is joined to the C-terminus  
 directly or through a linker capable of joining the N-  
 25 terminus to the C-terminus and having new C- and N-  
 termini at amino acids;

|       |       |                   |
|-------|-------|-------------------|
| 28-29 | 42-43 | 93-94             |
| 29-30 | 64-65 | 94-95             |
| 30-31 | 65-66 | 95-96             |
| 31-32 | 66-67 | 96-97             |
| 32-33 | 86-87 | 97-98             |
| 34-35 | 87-88 | 98-99             |
| 36-37 | 88-89 | 99-100            |
| 37-38 | 89-90 | 100-101           |
| 38-39 | 90-91 | 101-102           |
| 39-40 | 91-92 | 102-103           |
| 40-41 | 92-93 | respectively; and |
| 41-42 |       |                   |

additionally said flt3 receptor agonist polypeptide can  
 30 be immediately preceded by (methionine<sup>-1</sup>), (alanine<sup>-1</sup>) or  
 (methionine<sup>-2</sup>, alanine<sup>-1</sup>).

The more preferred breakpoints at which new C-  
 terminus and N-terminus can be made are 36-37, 37-38,  
 35 38-39, 39-40, 40-41, 41-42, 42-43, 64-65, 65-66, 66-67,

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86-87, 87-88, 88-89, 89-90, 90-91, 91-92, 92-93, 93-94,  
95,-96, 96-97, 97-98, 99-100 and 100-101

The most preferred breakpoints at which new C-  
5 terminus and N-terminus can be made are; 39-40, 65-66,  
89-90, 99-100 and 100-101.

The flt3 receptor agonists of the present invention  
may contain amino acid substitutions, deletions and/or  
10 insertions. It is also intended that the flt3 receptor  
agonists of the present invention may also have amino  
acid deletions at either/or both the N- and C- termini  
of the original protein and or deletions from the new N-  
and/or C-termini of the sequence rearranged proteins in  
15 the formulas shown above.

The flt3 receptor agonists of the present invention  
may contain amino acid substitutions, deletions and/or  
insertions.  
20

A preferred embodiment of the present invention the  
linker (L) joining the N-terminus to the C-terminus is a  
polypeptide selected from the group consisting of:

GlyGlyGlySer SEQ ID NO:38;  
25 GlyGlyGlySerGlyGlyGlySer SEQ ID NO:39;  
GlyGlyGlySerGlyGlyGlySerGlyGlyGlySer SEQ ID NO:40;  
SerGlyGlySerGlyGlySer SEQ ID NO:41;  
GluPheGlyAsnMet SEQ ID NO:42;  
GluPheGlyGlyAsnMet SEQ ID NO:43;  
30 GluPheGlyGlyAsnGlyGlyAsnMet SEQ ID NO:44;  
GlyGlySerAspMetAlaGly SEQ ID NO:45;  
SerGlyGlyAsnGly SEQ ID NO:46;  
SerGlyGlyAsnGlySerGlyGlyAsnGly SEQ ID NO:47;  
SerGlyGlyAsnGlySerGlyGlyAsnGlySerGlyGlyAsnGly SEQ  
35 ID NO:48;  
SerGlyGlySerGlySerGlyGlySerGly SEQ ID NO:49;

SerGlyGlySerGlySerGlyGlySerGlySerGlyGlySerGly SEQ  
 ID NO:50;  
 GlyGlyGlySerGlyGly SEQ ID NO:51;  
 GlyGlyGlySerGlyGlyGly SEQ ID NO:52;  
 5 GlyGlyGlySerGlyGlyGlySerGlyGly SEQ ID NO:53;  
 GlyGlyGlySerGlyGlyGlySerGlyGlyGlySerGly SEQ ID  
 NO:54;  
 GlyGlyGlySerGlyGlyGlySerGlyGlyGlySerGlyGlyGly SEQ  
 ID NO:55;  
 10 GlyGlyGlySerGlyGlyGlySerGlyGlyGlySerGlyGlyGlySerGly  
 GlyGlySerGly SEQ ID NO:56;  
 GlyGlyGlySerGlyGlyGlySerGlyGlyGlySerGlyGlyGlySerGly  
 GlyGlySerGlyGlyGlySerGlyGlyGlySerGly SEQ ID NO:148;  
 ProProProTrpSerProArgProLeuGlyAlaThrAlaProThrAlaGly  
 15 GlnProProLeu SEQ ID NO:149;  
 ProProProTrpSerProArgProLeuGlyAlaThrAlaProThr SEQ  
 ID NO:150; and  
 ValGluThrValPheHisArgValSerGlnAspGlyLeuLeuThrSer  
 SEQ ID NO:151.

20

The present invention also encompasses recombinant  
 human flt3 receptor agonists co-administered or  
 sequentially with one or more additional colony  
 stimulating factors (CSF) including, cytokines,  
 25 lymphokines, interleukins, hematopoietic growth factors  
 which include but are not limited to GM-CSF, G-CSF, c-  
 mpl ligand (also known as TPO or MGDF), M-CSF,  
 erythropoietin (FLT3), IL-1, IL-4, IL-2, IL-3, IL-5, IL-  
 6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-15,  
 30 LIF, human growth hormone, B-cell growth factor, B-cell  
 differentiation factor, eosinophil differentiation  
 factor and stem cell factor (SCF) also known as steel  
 factor or c-kit ligand (herein collectively referred to  
 as "factors"). These co-administered mixtures may be  
 35 characterized by having the usual activity of both of  
 the peptides or the mixture may be further characterized  
 by having a biological or physiological activity greater

than simply the additive function of the presence of the  
flt3 receptor agonists or the second colony stimulating  
factor alone. The co-administration may also provide an  
enhanced effect on the activity or an activity different  
5 from that expected by the presence of the flt3 ligand or  
the second colony stimulating factor. The co-  
administration may also have an improved activity  
profile which may include reduction of undesirable  
biological activities associated with native human flt3  
10 ligand. In addition to the list above, IL-3 variants  
taught in WO 94/12639 and WO 94/12638 fusion protein  
taught in WO 95/21197, and WO 95/21254 G-CSF receptor  
agonists disclosed in WO 97/12977, c-mpl receptor  
agonists disclosed in WO 97/12978, IL-3 receptor  
15 agonists disclosed in WO 97/12979 and multi-functional  
receptor agonists taught in WO 97/12985 can be co-  
administered with the polypeptides of the present  
invention. As used herein "IL-3 variants" refer to IL-3  
variants taught in WO 94/12639 and WO 94/12638. As used  
20 herein "fusion proteins" refer to fusion protein taught  
in WO 95/21197, and WO 95/21254. As used herein "G-CSF  
receptor agonists" refer to G-CSF receptor agonists  
disclosed in WO 97/12978. As used herein "c-mpl receptor  
agonists" refer to c-mpl receptor agonists disclosed in  
25 WO 97/12978. As used herein "IL-3 receptor agonists"  
refer to IL-3 receptor agonists disclosed in WO  
97/12979. As used herein "multi-functional receptor  
agonists" refer to multi-functional receptor agonists  
taught in WO 97/12985.

30

In addition, it is envisioned that *in vitro* uses  
would include the ability to stimulate bone marrow and  
blood cell activation and growth before the expanded  
35 cells are infused into patients. Another intended use is  
for the production of dendritic cells both *in vivo* and  
*ex vivo*.

Brief Description of the Figures

Figure 1 schematically illustrates the sequence  
5 rearrangement of a protein. The N-terminus (N) and the  
C-terminus (C) of the native protein are joined through  
a linker, or joined directly. The protein is opened at a  
breakpoint creating a new N-terminus (new N) and a new  
C-terminus (new-C) resulting in a protein with a new  
10 linear amino acid sequence. A rearranged molecule may be  
synthesized *de novo* as linear molecule and not go  
through the steps of joining the original N-terminus and  
the C-terminus and opening of the protein at the  
breakpoint.

15

Figure 2 shows a schematic of Method I, for  
creating new proteins in which the original N-terminus  
and C-terminus of the native protein are joined with a  
linker and different N-terminus and C-terminus of the  
20 protein are created. In the example shown the sequence  
rearrangement results in a new gene encoding a protein  
with a new N-terminus created at amino acid 97 of the  
original protein, the original C-terminus (a.a. 174)  
joined to the amino acid 11 (a.a. 1- 10 are deleted)  
25 through a linker region and a new C-terminus created at  
amino acid 96 of the original sequence.

Figure 3 shows a schematic of Method II, for  
creating new proteins in which the original N-terminus  
30 and C-terminus of the native protein are joined without  
a linker and different N-terminus and C-terminus of the  
protein are created. In the example shown the sequence  
rearrangement results in a new gene encoding a protein  
with a new N-terminus created at amino acid 97 of the  
35 original protein, the original C-terminus (a.a. 174)  
joined to the original N-terminus and a new C-terminus  
created at amino acid 96 of the original sequence.

Figure 4 shows a schematic of Method III, for creating new proteins in which the original N-terminus and C-terminus of the native protein are joined with a linker and different N-terminus and C-terminus of the protein are created. In the example shown the sequence rearrangement results in a new gene encoding a protein with a new N-terminus created at amino acid 97 of the original protein, the original C-terminus (a.a. 174) joined to amino acid 1 through a linker region and a new C-terminus created at amino acid 96 of the original sequence.

Figure 5a and 5b shows the DNA sequence encoding the 209 amino acid mature form of flt3 ligand from Lyman et al. (*Oncogene* **11**:1165-1172, 1995).

Figure 6 shows the DNA sequence encoding the 134 amino acid soluble form of flt3 ligand from Lyman et al. (*Oncogene* **11**:1165-1172, 1995).

Figure 7 shows the bioactivity of the flt3 receptor agonists pMON32320 and pMON32321 compared to recombinant native flt3 (Genzyme) in the MUTZ-2 cell proliferation assay. MT = mock transfection.

Detailed Description of the Invention

Flt3 receptor agonists of the present invention may be useful in the treatment of diseases characterized by decreased levels of hematopoietic cells.

A flt3 receptor agonist may be useful in the treatment or prevention of hematopoietic disorders. Many drugs may cause bone marrow suppression or hematopoietic deficiencies. Examples of such drugs are AZT, DDI, alkylating agents and anti-metabolites used in chemotherapy, antibiotics such as chloramphenicol, penicillin, gancyclovir, daunomycin and sulfa drugs, phenothiazones, tranquilizers such as meprobamate, analgesics such as aminopyrine and dipyrone, anti-convulsants such as phenytoin or carbamazepine, antithyroids such as propylthiouracil and methimazole and diuretics. flt3 receptor agonists may be useful in preventing or treating the bone marrow suppression or hematopoietic deficiencies which often occur in patients treated with these drugs.

Hematopoietic deficiencies may also occur as a result of viral, microbial or parasitic infections, burns and as a result of treatment for renal disease or renal failure, e.g., dialysis. The present peptide may be useful in treating such hematopoietic deficiency.

Another aspect of the present invention provides plasmid DNA vectors for use in the method of expression of these novel flt3 receptor agonists. These vectors contain the novel DNA sequences described above which code for the novel polypeptides of the invention. Appropriate vectors which can transform host cells capable of expressing the flt3 receptor agonists include expression vectors comprising nucleotide sequences coding for the flt3 receptor agonists joined to transcriptional and translational regulatory sequences which are selected according to the host cells used. Vectors incorporating modified sequences as described

above are included in the present invention and are useful in the production of the modified *flt3* receptor agonist polypeptides. The vector employed in the method also contains selected regulatory sequences in operative  
5 association with the DNA coding sequences of the invention and capable of directing the replication and expression thereof in selected host cells.

As another aspect of the present invention, there is provided a novel method for producing the novel  
10 family of human *flt3* receptor agonists. The method of the present invention involves culturing suitable cells or cell line, which has been transformed with a vector containing a DNA sequence coding for expression of the novel *flt3* receptor agonist polypeptide. Suitable cells  
15 or cell lines may include various strains of bacteria such as *E. coli*, yeast, mammalian cells, or insect cells may be utilized as host cells in the method of the present invention.

20 Other aspects of the present invention are methods and therapeutic compositions for treating the conditions referred to above. Such compositions comprise a therapeutically effective amount of one or more of the *flt3* receptor agonists of the present invention in a  
25 mixture with a pharmaceutically acceptable carrier. This composition can be administered either parenterally, intravenously or subcutaneously. When administered, the therapeutic composition for use in this invention is preferably in the form of a pyrogen-  
30 free, parenterally acceptable aqueous solution. The preparation of such a parenterally acceptable protein solution, having due regard to pH, isotonicity, stability and the like, is within the skill of the art.

35 The dosage regimen involved in a method for treating the above-described conditions will be determined by the attending physician considering

various factors which modify the action of drugs, e.g. the condition, body weight, sex and diet of the patient, the severity of any infection, time of administration and other clinical factors. Generally, a daily regimen may be in the range of 0.5 - 150 µg/kg of non-glycosylated flt3 receptor agonists protein per kilogram of body weight. Dosages would be adjusted relative to the activity of a given receptor agonist and it would not be unreasonable to note that dosage regimens may include doses as low as 0.1 microgram and as high as 1 milligram per kilogram of body weight per day. In addition, there may exist specific circumstances where dosages of flt3 receptor agonist would be adjusted higher or lower than the range of 0.5 - 150 micrograms per kilogram of body weight. These include co-administration with other CSF or growth factors; co-administration with chemotherapeutic drugs and/or radiation; the use of glycosylated flt3 receptor agonists; and various patient-related issues mentioned earlier in this section. As indicated above, the therapeutic method and compositions may also include co-administration with other human factors. A non-exclusive list of other appropriate hematopoietins, CSFs and interleukins for simultaneous or serial co-administration with the polypeptides of the present invention includes GM-CSF, G-CSF, c-mpl ligand (also known as TPO or MGDF), M-CSF, erythropoietin (FLT3), IL-1, IL-4, IL-2, IL-3, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-15, LIF, human growth hormone, B-cell growth factor, B-cell differentiation factor, eosinophil differentiation factor and stem cell factor (SCF) also known as steel factor or c-kit ligand (herein collectively referred to as "factors"), or combinations thereof. In addition to the list above, IL-3 variants taught in WO 94/12639 and WO 94/12638 fusion protein taught in WO 95/21197, and WO 95/21254 G-CSF receptor agonists disclosed in WO 97/12977, c-mpl

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receptor agonists disclosed in WO 97/12978, IL-3  
receptor agonists disclosed in WO 97/12979 and multi-  
functional receptor agonists taught in WO 97/12985 can  
be co-administered with the polypeptides of the present  
5 invention.

The *flt3* receptor agonists of the present invention  
may be useful in the mobilization of hematopoietic  
progenitors and stem cells in peripheral blood.  
10 Peripheral blood derived progenitors have been shown to  
be effective in reconstituting patients in the setting  
of autologous marrow transplantation. Hematopoietic  
growth factors, including G-CSF and GM-CSF, have been  
shown to enhance the number of circulating progenitors  
15 and stem cells in the peripheral blood. This has  
simplified the procedure for peripheral stem cell  
collection and dramatically decreased the cost of the  
procedure by decreasing the number of pheresis required.  
The *flt3* receptor agonist of the present invention may  
20 be useful in mobilization of stem cells and further  
enhance the efficacy of peripheral stem cell  
transplantation.

The *flt3* receptor agonists of the present invention  
25 may also be useful in the ex vivo expansion of  
hematopoietic progenitors. Colony stimulating factors  
(CSFs), such as G-CSF, have been administered alone, co-  
administered with other CSFs, or in combination with  
bone marrow transplants subsequent to high dose  
30 chemotherapy to treat the neutropenia and which is often  
the result of such treatment. However the period of  
severe neutropenia may not be totally eliminated. The  
myeloid lineage, which is comprised of monocytes  
(macrophages), granulocytes (including neutrophils) and  
35 megakaryocytes, is critical in preventing infections and  
bleeding which can be life-threatening. Neutropenia may  
also be the result of disease, genetic disorders, drugs,

toxins, radiation and many therapeutic treatments such as conventional oncology therapy.

Bone marrow transplants have been used to treat this patient population. However, several problems are associated with the use of bone marrow to reconstitute a compromised hematopoietic system including: 1) the number of stem cells in bone marrow or other tissues, such as spleen or peripheral blood, is limited, 2) Graft Versus Host Disease, 3) graft rejection and 4) possible contamination with tumor cells. Stem cells and progenitor cells make up a very small percentage of the nucleated cells in the bone marrow, spleen and peripheral blood. It is clear that a dose response exists such that a greater number of multipotential hematopoietic progenitors will enhance hematopoietic recovery. Therefore, the in vitro expansion of stem cells should enhance hematopoietic recovery and patient survival. Bone marrow from an allogeneic donor has been used to provide bone marrow for transplant. However, Graft Versus Host Disease and graft rejection limit bone marrow transplantation even in recipients with HLA-matched sibling donors. An alternative to allogeneic bone marrow transplants is autologous bone marrow transplants. In autologous bone marrow transplants, some of the patient's own marrow is harvested prior to myeloablative therapy, e.g. high dose chemotherapy, and is transplanted back into the patient afterwards. Autologous transplants eliminate the risk of Graft Versus Host Disease and graft rejection. However, autologous bone marrow transplants still present problems in terms of the limited number of stem cells in the marrow and possible contamination with tumor cells. The limited number of multipotential hematopoietic progenitors may be overcome by ex-vivo expansion of the multipotential hematopoietic progenitors. In addition, stem cells can be specifically isolated based on the presence of specific surface

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antigens such as CD34+ in order to decrease tumor cell contamination of the marrow graft.

- The following patents contain further details on
- 5 separating stem cells, CD34+ cells, culturing the cells with hematopoietic factors, the use of the cells for the treatment of patients with hematopoietic disorders and the use of hematopoietic factors for cell expansion and gene therapy.
- 10 5,061,620 relates to compositions comprising human hematopoietic stem cells provided by separating the stem cells from dedicated cells.
- 15 5,199,942 describes a method for autologous hematopoietic cell transplantation comprising: (1) obtaining hematopoietic progenitor cells from a patient; (2) ex-vivo expansion of cells with a growth factor selected from the group consisting of IL-3, flt3 ligand,
- 20 c-kit ligand, GM-CSF, IL-1, GM-CSF/IL-3 fusion protein and combinations thereof; (3) administering cellular preparation to a patient.
- 5,240,856 relates to a cell separator that includes an
- 25 apparatus for automatically controlling the cell separation process.
- WO 91/16116 describes devices and methods for selectively isolating and separating target cells from a
- 30 mixture of cells.
- WO 91/18972 describes methods for in vitro culturing of bone marrow, by incubating suspension of bone marrow cells, using a hollow fiber bioreactor.
- 35 WO 92/18615 relates to a process for maintaining and expanding bone marrow cells, in a culture medium

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containing specific mixtures of cytokines, for use in transplants.

WO 93/08268 describes a method for selectively expanding  
5 stem cells, comprising the steps of (a) separating CD34+ stem cells from other cells and (b) incubating the separated cells in a selective medium, such that the stem cells are selectively expanded.

10 WO 93/18136 describes a process for in vitro support of mammalian cells derived from peripheral blood.

WO 93/18648 relates to a composition comprising human neutrophil precursor cells with a high content of  
15 myeloblasts and promyelocytes for treating genetic or acquired neutropenia.

WO 94/08039 describes a method of enrichment for human hematopoietic stem cells by selection for cells which  
20 express c-kit protein.

WO 94/11493 describes a stem cell population that are CD34+ and small in size, which are isolated using a counterflow elutriation method.

25 WO 94/27698 relates to a method combining immunoaffinity separation and continuous flow centrifugal separation for the selective separation of a nucleated heterogeneous cell population from a heterogeneous cell  
30 mixture.

WO 94/25848 describes a cell separation apparatus for collection and manipulation of target cells.

35 The long term culturing of highly enriched CD34+ precursors of hematopoietic progenitor cells from human bone marrow in cultures containing IL-1 $\alpha$ , IL-3, IL-6 or

GM-CSF is discussed in Brandt et al (*J. Clin. Invest.* 86:932-941, 1990).

One aspect of the present invention provides a method for selective ex-vivo expansion of stem cells. The term "stem cell" refers to the multipotential hematopoietic cells as well as early myeloid progenitor and precursors cells which can be isolated from bone marrow, spleen or peripheral blood. The term "expansion" refers to the proliferation and differentiation of the cells. The present invention provides a method for selective ex-vivo expansion of stem cells, comprising the steps of; (a) separating stem cells from other cells, (b) culturing the separated stem cells with a selective medium which contains a flt3 receptor agonist and optionally a second colony stimulating factor, and (c) harvesting the cultured stems cells. Stem cells, as well as committed progenitor cells destined to become neutrophils, erythrocytes, platelets, etc., may be distinguished from most other cells by the presence or absence of particular progenitor marker antigens, such as CD34, that are present on the surface of these cells and/or by morphological characteristics. The phenotype for a highly enriched human stem cell fraction is reported as CD34+, Thy-1+ and lin-, but it is to be understood that the present invention is not limited to the expansion of this stem cell population. The CD34+ enriched human stem cell fraction can be separated by a number of reported methods, including affinity columns or beads, magnetic beads or flow cytometry using antibodies directed to surface antigens such as the CD34+. Further, physical separation methods such as counterflow elutriation may be used to enrich hematopoietic progenitors. The CD34+ progenitors are heterogeneous, and may be divided into several sub-populations characterized by the presence or absence of co-expression of different lineage associated cell

surface associated molecules. The most immature progenitor cells do not express any known lineage associated markers, such as HLA-DR or CD38, but they may express CD90(thy-1). Other surface antigens such as  
5 CD33, CD38, CD41, CD71, HLA-DR or c-kit can also be used to selectively isolate hematopoietic progenitors. The separated cells can be incubated in selected medium in a culture flask, sterile bag or in hollow fibers. Various colony stimulating factors may be utilized in order to  
10 selectively expand cells. Representative factors that have been utilized for ex-vivo expansion of bone marrow include, c-kit ligand, IL-3, G-CSF, GM-CSF, IL-1, IL-6, IL-11, flt3 ligand or combinations thereof. The proliferation of the stem cells can be monitored by  
15 enumerating the number of stem cells and other cells, by standard techniques (e.g. hemacytometer, CFU, LTCIC) or by flow cytometry prior and subsequent to incubation.

Several methods for ex-vivo expansion of stem cells  
20 have been reported utilizing a number of selection methods and expansion using various colony stimulating factors including c-kit ligand (Brandt et al., *Blood* **83**:1507-1514, 1994; McKenna et al., *Blood* **86**:3413-3420, 1995), IL-3 (Brandt et al., *Blood* **83**:1507-1514, 1994;  
25 Sato et al., *Blood* **82**:3600-3609, 1993), G-CSF (Sato et al., *Blood* **82**:3600-3609, 1993), GM-CSF (Sato et al., *Blood* **82**:3600-3609, 1993), IL-1 (Muench et al., *Blood* **81**:3463-3473, 1993), IL-6 (Sato et al., *Blood* **82**:3600-3609, 1993), IL-11 (Lemoli et al., *Exp. Hem.* **21**:1668-  
30 1672, 1993; Sato et al., *Blood* **82**:3600-3609, 1993), flt3 ligand (McKenna et al., *Blood* **86**:3413 3420, 1995) and/or combinations thereof (Brandt et al., *Blood* **83**:1507 1514, 1994; Haylock et al., *Blood* **80**:1405-1412, 1992, Koller et al., *Biotechnology* **11**:358-363, 1993; Lemoli et al.,  
35 *Exp. Hem.* **21**:1668-1672, 1993), McKenna et al., *Blood* **86**:3413-3420, 1995; Muench et al., *Blood* **81**:3463-3473, 1993; Patchen et al., *Biotherapy* **7**:13-26, 1994; Sato et

al., *Blood* **82**:3600-3609, 1993; Smith et al., *Exp. Hem.* **21**:870-877, 1993; Steen et al., *Stem Cells* **12**:214-224, 1994; Tsujino et al., *Exp. Hem.* **21**:1379-1386, 1993).

Among the individual colony stimulating factors, hIL-3  
5 has been shown to be one of the most potent in expanding peripheral blood CD34+ cells (Sato et al., *Blood* **82**:3600-3609, 1993; Kobayashi et al., *Blood* **73**:1836-1841, 1989). However, no single factor has been shown to be as effective as the combination of multiple factors.  
10 The present invention provides methods for ex vivo expansion that utilize novel flt3 receptor agonists.

Another aspect of the invention provides methods of sustaining and/or expanding hematopoietic precursor  
15 cells which includes inoculating the cells into a culture vessel which contains a culture medium that has been conditioned by exposure to a stromal cell line such as HS-5 (WO 96/02662, Roecklein and Torok-Strob, *Blood* **85**:997-1105, 1995) that has been supplemented with a  
20 flt3 receptor agonist of the present invention.

It is also envisioned that uses of flt3 receptor agonists of the present invention would include blood banking applications, where the flt3 receptor agonists  
25 are given to a patient to increase the number of blood cells and blood products are removed from the patient, prior to some medical procedure, and the blood products are stored and transfused back into the patient after the medical procedure. Additionally, it is envisioned  
30 that uses of flt3 receptor agonists would include giving the flt3 receptor agonists to a blood donor prior to blood donation to increase the number of blood cells, thereby allowing the donor to safely give more blood.

35 Another projected clinical use of growth factors has been in the in vitro activation of hematopoietic progenitors and stem cells for gene therapy. Due to the

long life-span of hematopoietic progenitor cells and the distribution of their daughter cells throughout the entire body, hematopoietic progenitor cells are good candidates for ex vivo gene transfection. In order to

5 have the gene of interest incorporated into the genome of the hematopoietic progenitor or stem cell one needs to stimulate cell division and DNA replication.

Hematopoietic stem cells cycle at a very low frequency which means that growth factors may be useful to promote

10 gene transduction and thereby enhance the clinical prospects for gene therapy. Potential applications of gene therapy (review Crystal, *Science* **270**:404-410, 1995) include; 1) the treatment of many congenital metabolic disorders and immunodeficiencies (Kay and Woo, *Trends*  
15 *Genet.* **10**:253-257, 1994), 2) neurological disorders (Friedmann, *Trends Genet.* **10**:210-214, 1994), 3) cancer (Culver and Blaese, *Trends Genet.* **10**:174-178, 1994) and 4) infectious diseases (Gilboa and Smith, *Trends Genet.* **10**:139-144, 1994).

20 There are a variety of methods, known to those with skill in the art, for introducing genetic material into a host cell. A number of vectors, both viral and non-viral have been developed for transferring therapeutic genes into primary cells. Viral based vectors include;

25 1) replication deficient recombinant retrovirus (Boris-Lawrie and Temin, *Curr. Opin. Genet. Dev.* **3**:102-109, 1993; Boris-Lawrie and Temin, *Annal. New York Acad. Sci.* **716**:59-71, 1994; Miller, *Current Top. Microbiol. Immunol.* **158**:1-24, 1992) and replication-deficient  
30 recombinant adenovirus (Berkner, *BioTechniques* **6**:616-629, 1988; Berkner, *Current Top. Microbiol. Immunol.* **158**:39-66, 1992; Brody and Crystal, *Annal. New York Acad. Sci.* **716**:90-103, 1994). Non-viral based vectors include protein/DNA complexes (Cristiano et al., *PNAS*  
35 *USA.* **90**:2122-2126, 1993; Curiel et al., *PNAS USA* **88**:8850-8854, 1991; Curiel, *Annal. New York Acad. Sci.* **716**:36-58, 1994), electroporation and liposome mediated

delivery such as cationic liposomes (Farhood et al.,  
*Annal. New York Acad. Sci.* **716**:23-35, 1994).

The present invention provides an improvement to  
the existing methods of expanding hematopoietic cells,  
5 into which new genetic material has been introduced, in  
that it provides methods utilizing flt3 receptor  
agonists that may have improved biological activity  
and/or physical properties.

10 Another intended use of the flt-3 receptor agonists  
of the present invention is for the generation of larger  
numbers of dendritic cells, from precursors, to be used  
as adjuvants for immunization. Dendritic cells play a  
crucial role in the immune system. They are the  
15 professional antigen-presenting cells most efficient in  
the activation of resting T cells and are the major  
antigen-presenting cells for activation of naïve T cells  
*in vivo* and, thus, for initiation of primary immune  
responses. They efficiently internalize, process and  
20 present soluble tumor-specific antigens (Ag). Dendritic  
cells have the unique capacity to cluster naïve T cells  
and to respond to Ag encounter by rapid up-regulation of  
the expression of major histocompatibility complex (MHC)  
and co-stimulatory molecules, the production of  
25 cytokines and migration towards lymphatic organs. Since  
dendritic cells are of central importance for  
sensitizing the host against a neoantigen for CD4-  
dependent immune responses, they may also play a crucial  
role in the generation and regulation of tumor immunity.

30 Dendritic cells originate from a bone marrow CD34+  
precursor common to granulocytes and macrophages, and  
the existence of a separate dendritic cell colony-  
forming unit (CFU-DC) that give rise to pure dendritic  
35 cell colonies has been established in humans. In  
addition, a post-CFU CD14+ intermediate has been  
described with the potential to differentiate along the  
dendritic cell or the macrophage pathway under distinct

cytokine conditions. This bipotential precursor is present in the bone marrow, cord blood and peripheral blood. Dendritic cells can be isolated by the cell specific marker, CD83, which is expressed on mature  
5 dendritic cells, to delineate the maturation of cultured dendritic cells.

Dendritic cells based strategies provide a method for enhancing immune response against tumors and  
10 infectious agents. AIDS is another disease for which dendritic cell based therapies can be used, since dendritic cells can play a major role in promoting HIV-1 replication. An immunotherapy requires the generation of dendritic cells from cancer patients, their *in vitro*  
15 exposure to tumor Ag, derived from surgically removed tumor masses, and reinjection of these cells into the tumor patients. Relatively crude membrane preparations of tumor cells will suffice as sources of tumor antigen, avoiding the necessity for molecular identification of  
20 the tumor antigen. The tumor antigen may also be synthetic peptides, carbohydrates, or nucleic acid sequences. In addition, concomitant administration of cytokines such as the flt-3 receptor agonists of the present invention may further facilitate the induction  
25 of tumor immunity. It is foreseen that the immunotherapy can be in an *in vivo* setting, wherein the flt-3 receptor agonists of the present invention is administered to a patient, having a tumor, alone or with other hematopoietic growth factors to increase the number of  
30 dendritic cells and endogenous tumor antigen is presented on the dendritic cells. It is also envisioned that *in vivo* immunotherapy can be with exogenous antigen. It is also envisioned that the immunotherapy treatment may include the mobilization of dendritic cell  
35 precursors or mature dendritic, by administering the flt-3 receptor agonists of the present invention alone or with other hematopoietic growth factors to the patient, removing the dendritic cell precursors or

mature dendritic cells from the patient, exposing the dendritic cells to antigen and returning the dendritic cells to the patient. Furthermore, the dendritic cells that have been removed can be cultured *ex vivo* with the  
5 flt-3 receptor agonists of the present invention alone or with other hematopoietic growth factors to increase the number of dendritic cells prior to exposure to antigen. Dendritic cells based strategies also provide a method for reducing the immune response in auto-immune  
10 diseases.

Studies on dendritic cells have been greatly hampered by difficulties in preparing the cells in sufficient numbers and in a reasonably pure form. In an  
15 ex-vivo cell expansion setting, granulocyte-macrophage colony-stimulating factor (GM-CSF) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) cooperate in the *ex vivo* generation of dendritic cells from hematopoietic progenitors (CD34+ cells) retrieved from bone marrow, cord blood, or  
20 peripheral blood and flk-2/flt-3 ligand and c-kit ligand (stem cell factor [SCF]) synergize to enhance the GM-CSF plus TNF- $\alpha$  induced generation of dendritic cells (Siena, S. *et al. Experimental Hematology* **23**:1463-1471, 1995). Also provide is a method of *ex vivo* expansion of  
25 dendritic cell precursors or mature dendritic cells using the flt-3 receptor agonists of the present invention to provide sufficient quantities of dendritic cells for immunotherapy.

### 30 Determination of the Linker

The length of the amino acid sequence of the linker can be selected empirically or with guidance from structural information, or by using a combination of the  
35 two approaches.

When no structural information is available, a small series of linkers can be prepared for testing

using a design whose length is varied in order to span a range from 0 to 50 Å and whose sequence is chosen in order to be consistent with surface exposure (hydrophilicity, Hopp & Woods, *Mol. Immunol.* **20**: 483-489, 1983; Kyte & Doolittle, *J. Mol. Biol.* **157**:105-132, 1982; solvent exposed surface area, Lee & Richards, *J. Mol. Biol.* **55**:379-400, 1971) and the ability to adopt the necessary conformation without deranging the configuration of the flt3 receptor agonist (conformationally flexible; Karplus & Schulz, *Naturwissenschaften* **72**:212-213, (1985). Assuming an average of translation of 2.0 to 3.8 Å per residue, this would mean the length to test would be between 0 to 30 residues, with 0 to 15 residues being the preferred range. Exemplary of such an empirical series would be to construct linkers using a cassette sequence such as Gly-Gly-Gly-Ser repeated n times, where n is 1, 2, 3 or 4. Those skilled in the art will recognize that there are many such sequences that vary in length or composition that can serve as linkers with the primary consideration being that they be neither excessively long nor short (cf., Sandhu, *Critical Rev. Biotech.* **12**: 437-462, 1992); if they are too long, entropy effects will likely destabilize the three-dimensional fold, and may also make folding kinetically impractical, and if they are too short, they will likely destabilize the molecule because of torsional or steric strain.

Those skilled in the analysis of protein structural information will recognize that using the distance between the chain ends, defined as the distance between the c-alpha carbons, can be used to define the length of the sequence to be used, or at least to limit the number of possibilities that must be tested in an empirical selection of linkers. They will also recognize that it is sometimes the case that the positions of the ends of the polypeptide chain are ill-defined in structural

models derived from x-ray diffraction or nuclear magnetic resonance spectroscopy data, and that when true, this situation will therefore need to be taken into account in order to properly estimate the length of the linker required. From those residues whose positions are well defined are selected two residues that are close in sequence to the chain ends, and the distance between their c-alpha carbons is used to calculate an approximate length for a linker between them. Using the calculated length as a guide, linkers with a range of number of residues (calculated using 2 to 3.8Å per residue) are then selected. These linkers may be composed of the original sequence, shortened or lengthened as necessary, and when lengthened the additional residues may be chosen to be flexible and hydrophilic as described above; or optionally the original sequence may be substituted for using a series of linkers, one example being the Gly-Gly-Gly-Ser cassette approach mentioned above; or optionally a combination of the original sequence and new sequence having the appropriate total length may be used.

#### Determination of the Amino and Carboxyl Termini of flt3 Receptor Agonists

Sequences of flt3 receptor agonists capable of folding to biologically active states can be prepared by appropriate selection of the beginning (amino terminus) and ending (carboxyl terminus) positions from within the original polypeptide chain while using the linker sequence as described above. Amino and carboxyl termini are selected from within a common stretch of sequence, referred to as a breakpoint region, using the guidelines described below. A novel amino acid sequence is thus generated by selecting amino and carboxyl termini from within the same breakpoint region. In many cases the selection of the new termini will be such that the

original position of the carboxyl terminus immediately preceded that of the amino terminus. However, those skilled in the art will recognize that selections of termini anywhere within the region may function, and that these will effectively lead to either deletions or additions to the amino or carboxyl portions of the new sequence.

It is a central tenet of molecular biology that the primary amino acid sequence of a protein dictates folding to the three-dimensional structure necessary for expression of its biological function. Methods are known to those skilled in the art to obtain and interpret three-dimensional structural information using x-ray diffraction of single protein crystals or nuclear magnetic resonance spectroscopy of protein solutions. Examples of structural information that are relevant to the identification of breakpoint regions include the location and type of protein secondary structure (alpha and 3-10 helices, parallel and anti-parallel beta sheets, chain reversals and turns, and loops; Kabsch & Sander, *Biopolymers* **22**: 2577-2637, 1983; the degree of solvent exposure of amino acid residues, the extent and type of interactions of residues with one another (Chothia, *Ann. Rev. Biochem.* **53**:537-572; 1984) and the static and dynamic distribution of conformations along the polypeptide chain (Alber & Mathews, *Methods Enzymol.* **154**: 511-533, 1987). In some cases additional information is known about solvent exposure of residues; one example is a site of post-translational attachment of carbohydrate which is necessarily on the surface of the protein. When experimental structural information is not available, or is not feasible to obtain, methods are also available to analyze the primary amino acid sequence in order to make predictions of protein tertiary and secondary structure, solvent accessibility and the occurrence of turns and loops. Biochemical methods are also sometimes applicable for empirically

determining surface exposure when direct structural methods are not feasible; for example, using the identification of sites of chain scission following limited proteolysis in order to infer surface exposure  
5 (Gentile & Salvatore, *Eur. J. Biochem.* **218**:603-621, 1993). Thus using either the experimentally derived structural information or predictive methods (e.g., Srinivisan & Rose *Proteins: Struct., Funct. & Genetics*,  
10 **22**: 81-99, 1995) the parental amino acid sequence is inspected to classify regions according to whether or not they are integral to the maintenance of secondary and tertiary structure. The occurrence of sequences within regions that are known to be involved in periodic  
15 secondary structure (alpha and 3-10 helices, parallel and anti-parallel beta sheets) are regions that should be avoided. Similarly, regions of amino acid sequence that are observed or predicted to have a low degree of solvent exposure are more likely to be part of the so-called hydrophobic core of the protein and should also  
20 be avoided for selection of amino and carboxyl termini. In contrast, those regions that are known or predicted to be in surface turns or loops, and especially those regions that are known not to be required for biological activity, are the preferred sites for location of the  
25 extremes of the polypeptide chain. Continuous stretches of amino acid sequence that are preferred based on the above criteria are referred to as a breakpoint region.

TABLE 1  
OLIGONUCLEOTIDES

|    |         |                                                                                |
|----|---------|--------------------------------------------------------------------------------|
| 5  | NCOFLT  | CTGACCATGGCNACCCAGGACTGCTCCTTCCAA SEQ ID NO:57;                                |
|    | HIND160 | ACTGAAGCTTAGGGCTGACACTGCAGCTCCAG SEQ ID NO:58;                                 |
|    | HIND165 | ACTGAAGCTTACAGGGTTGAGGAGTCGGGCTG SEQ ID NO:59;                                 |
| 10 | FL23For | GACTGCCATGGCNACYCAGGAYTGYTCYTTYCAACACAGCCCCATC<br>SEQ ID NO:60;                |
| 15 | FH3AFor | GACTGCCATGGCNACYCAGGAYTGYTCYTTYCAACACAGCCCCATC<br>SEQ ID NO:61;                |
|    | SCF.REV | TGTCCAAACTCATCAATGTATC SEQ ID NO:62;                                           |
|    | 39FOR   | CATGGCCATGGCCGACGAGGAGCTCTGCGGGGGCCTCT SEQ ID NO:63;                           |
| 20 | 39REV   | GCTAGAAGCTTACTGCAGGTTGGAGGCCACGGTGAC SEQ ID NO:64;                             |
| 25 | 65FOR   | CATGGCCATGGCCTCCAAGATGCAAGGCTTGCTGGAGC SEQ ID NO:65;                           |
|    | 65REV   | GCTAGAAGCTTACCCAGCGACAGTCTTGAGCCGCTC SEQ ID NO:66;                             |
|    | 89FOR   | CATGGCCATGGCCCCCCCCAGCTGTCTTCGCTTCGT SEQ ID NO:67;                             |
|    | 89REV   | GCTAGAAGCTTAGGGCTGAAAGGCACATTTGGTGACA SEQ ID NO:68;                            |
| 30 | L5A     | CCCTGTCTGGCGGCAACGGCACCCAGGACTGCTCCTTCCAAC<br>SEQ ID NO:69;                    |
| 35 | L10A    | GCGGTAACGGCAGTGGAGGTAATGGCACCCAGGACTGCTCCTTCCAAC<br>SEQ ID NO:70;              |
|    | L15A    | ACGGCAGTGGTGGCAATGGGAGCGGCGGAAATGGAACCCAGGACTGCTCCT<br>TCCAAC SEQ ID NO:71;    |
|    | L5B     | GTGCCGTTGCCGCCAGACAGGGTTGAGGAGTCGGGCTG SEQ ID NO:72;                           |
| 40 | L10B    | ATTACCTCCACTGCCGTTACCGCCTGACAGGGTTGAGGAGTCGGGCTG<br>SEQ ID NO:73;              |
| 45 | L15B    | GCTCCCATTGCCACCACTGCCGTTACCTCCAGACAGGGTTGAGGA<br>GTCGGGCTG SEQ ID NO:74;       |
|    | L15C    | GATGAGGATCCGGTGGCAATGGGAGCGGCGGAAATGGAACCCAGG<br>ACTGCTCCTTCCACC SEQ ID NO:75; |
| 50 | L15D    | GATGACGGATCCGTTACCTCCAGACAGGGTTGAGGAGTCGGGCTG<br>SEQ ID NO:76;                 |
|    | L15E    | GATGACGGATCCGGAGGTAATGGCACCCAGGACTGCTCCTTCCAAC<br>SEQ ID NO:77;                |

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339FOR2 GACTGCCATGGCCGACGAGGAGCTCTGCG SEQ ID NO:78;

339REV2 GACTCAAGCTTACTGCAGGTTGGAGGCC SEQ ID NO:79;

5 339-10FOR3 GACTCGGGATCCGGAGGTTCTGGCACCCAGGACTGCTCC SEQ ID NO:80;

339-15FOR2 GACTGGGATCCGGTGGCAGTGGGAGCGGCGGATCTGGAACC SEQ ID NO:81;

10 339REV3 GACTTGGGATCCACTACCTCCAGACAGGGTTGAGGAGTC SEQ ID NO:82;

FLN3 ACTGACGGATCCACCGCCCAGGGTTGAGGAGTCGGGCTG SEQ ID NO:83;

FLN7 ACTGACGGATCCACCTCCTGACCCACCGCCCAGGGTTGAGGAGTCGGGCTG  
SEQ ID NO:84;

15 FLN11 ACTGACGGATCCACCTCCTGACCCACCTCCTGACCCACCGCCCAG  
GGTTGAGGAGTCGGGCTG SEQ ID NO:85;

C-term ACGTAAAGCTTACAGGGTTGAGGAGTCG SEQ ID NO:86;

20 FLC3 GTCAGTGGATCCGGAGGTACCCAGGACTGCTCCTTCCAAC SEQ ID NO:87;

FLC4 GTCAGTGGATCCGGAGGTGGCACCCAGGACTGCTCCTTCCAAC  
SEQ ID NO:88;

25 FLC10 GTCAGTGGATCCGGAGGTGGCTCAGGGGGAGGTAGTGGTACCCAG  
GACTGCTCCTTCCAAC SEQ ID NO:89;

Flt36 GTTGCCATGGCNCNAAYCTGCARGAYGARGARCTGTGCGGGGGCCTCTGG  
CGGCTG SEQ ID NO:90;

30 Flt37 GTTGCCATGGCNAAYCTGCARGAYGARGARCTGTGYGGGGGCCTCTGGCG  
GCTGGTC SEQ ID NO:91;

35 Flt38 GTTGCCATGGCNC'TGCARGAYGARGARCTGTGYGGYGGCCTCTGGCGGCTG  
GTCCTG SEQ ID NO:92;

Flt39 GTTGCCATGGCNCARGAYGARGARCTGTGYGGYGGYCTCTGGCGGCTGGTC  
CTGGCA SEQ ID NO:93;

40 Flt40 GTTGCCATGGCNGAYGARGARCTGTGYGGYGGYCTCTGGCGGCTGGTCCTG  
GCACAG SEQ ID NO:94;

Flt41 GTTGCCATGGCNGARGARCTGTGYGGYGGYCTCTGGCGGCTGGTCCTGGCA  
CAGCGC SEQ ID NO:95;

45 Flt42 GTTGCCATGGCNGARCTGTGYGGYGGYCTGTGGCGYCTGGTCCTGGCACAG  
CGCTGG SEQ ID NO:96;

50 Flt43 GTTGCCATGGCNC'TGTGYGGYGGYCTGTGGCGYCTGGTCCTGGCACAGCGC  
TGGATG SEQ ID NO:97;

36REV TATGCAAGCTTAGGCCACGGTGAAGTGGTA SEQ ID NO:98;

55 37REV TATGCAAGCTTAGGAGGCCACGGTGAAGTGG SEQ ID NO:99;

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|    |       |                                               |
|----|-------|-----------------------------------------------|
|    | 38REV | TATGCAAGCTTAGTTGGAGGCCACGGTGAC SEQ ID NO:100; |
|    | 39REV | TATGCAAGCTTACAGGTTGGAGGCCACGGT SEQ ID NO:101; |
| 5  | 40REV | TATGCAAGCTTACTGCAGGTTGGAGGCCAC SEQ ID NO:102; |
|    | 41REV | TATGCAAGCTTAGTCCTGCAGGTTGGAGGC SEQ ID NO:103; |
| 10 | 42REV | TATGCAAGCTTACTCGTCCTGCAGGTTGGA SEQ ID NO:104; |
|    | 43REV | TATGCAAGCTTACTCCTCGTCCTGCAGGTT SEQ ID NO:105; |

TABLE 2  
DNA sequences

5 pMON30237.seq

GCCACCCAGGACTGCTCCTTCCAACACAGCCCCATCTCCTCCGACTTCGC  
 TGTCAAAATCCGTGAGCTGTCTGACTACCTGCTTCAAGATTACCCAGTCA  
 CCGTGCCCTCCAACCTGCAGGACGAGGAGCTCTGCGGGGCGCTCTGGCGG  
 CTGGTCCTGGCACAGCGCTGGATGGAGCGGCTCAAGACTGTCGCTGGGTC  
 10 CAAGATGCAAGGCTTGCTGGAGCGCGTGAACACGGAGATACACTTTGTCA  
 CCAAATGTGCCTTTTCAGCCCCCCCCAGCTGTCTTCGCTTCGTCCAGACC  
 AACATCTCCCGCCTCCTGCAGGAGACCTCCGAGCAGCTGGTGGCGCTGAA  
 GCCCTGGATCACTCGCCAGAACTTCTCCCGGTGCCTGGAGCTGCAGTGTC  
 AGCCC SEQ ID NO:106;

15

pMON30238.seq

GCCACCCAGGACTGCTCCTTCCAACACAGCCCCATCTCCTCCGACTTCGC  
 20 TGTCAAAATCCGTGAGCTGTCTGACTACCTGCTTCAAGATTACCCAGTCA  
 CCGTGCCCTCCAACCTGCAGGACGAGGAGCTCTGCGGGGCGCTCTGGCGG  
 CTGGTCCTGGCACAGCGCTGGATGGAGCGGCTCAAGACTGTCGCTGGGTC  
 CAAGATGCAAGGCTTGCTGGAGCGCGTGAACACGGAGATACACTTTGTCA  
 CCAAATGTGCCTTTTCAGCCCCCCCCAGCTGTCTTCGCTTCGTCCAGACC  
 25 AACATCTCCCGCCTCCTGCAGGAGACCTCCGAGCAGCTGGTGGCGCTGAA  
 GCCCTGGATCACTCGCCAGAACTTCTCCCGGTGCCTGGAGCTGCAGTGTC  
 AGCCCGACTCCTCAACCCTG SEQ ID NO:107;

30

pMON30239.seq

GCCACCCAGGACTGCTCCTTCCAACACAGCCCCATCTCCTCCGACTTCGC  
 TGTCAAAATCCGTGAGCTGTCTGACTACCTGCTTCAAGATTACCCAGTCA  
 CCGTGCCCTCCAACCTGCAGGACGAGGAGCTCTGCGGGGCGCTCTGGCGG  
 35 CTGGTCCTGGCACAGCGCTGGATGGAGCGGCTCAAGACTGTCGCTGGGTC  
 CAAGATGCAAGGCTTGCTGGAGCGCGTGAACACGGAGATACACTTTGTCA  
 CCAAATGTGCCTTTTCAGGAGACCTCCGAGCAGCTGGTGGCGCTGAAGCCC  
 TGGATCACTCGCCAGAACTTCTCCCGGTGCCTGGAGCTGCAGTGTCAGCC  
 CGACTCCTCAACCCTG SEQ ID NO:108;

40

pMON32329.seq

GGAACCTCAGGATTGTTCTTTCCAACACAGCCCCATCTCCTCCGACTTCGC  
 45 TGTCAAAATCCGTGAGCTGTCTGACTACCTGCTTCAAGATTACCCAGTCA  
 CCGTGCCCTCCAACCTGCAGGACGAGGAGCTCTGCGGGGCGCTCTGGCGG  
 CTGGTCCTGGCACAGCGCTGGATGGAGCGGCTCAAGACTGTCGCTGGGTC  
 CAAGATGCAAGGCTTGCTGGAGCGCGTGAACACGGAGATACACTTTGTCA  
 CCAAATGTGCCTTTTCAGCCCCCCCCAGCTGTCTTCGCTTCGTCCAGACC  
 50 AACATCTCCCGCCTCCTGCAGGAGACCTCCGAGCAGCTGGTGGCGCTGAA  
 GCCCTGGATCACTCGCCAGAACTTCTCCCGGTGCCTGGAGCTGCAGTGTC  
 AGCCC SEQ ID NO:109;

55

pMON32330.seq

GGTACCCAGGATTGTTCTTTCCAACACAGCCCCATCTCCTCCGACTTCGC  
 TGTCAAAATCCGTGAGCTGTCTGACTACCTGCTTCAAGATTACCCAGTCA  
 CCGTGGCCTCCAACCTGCAGGACGAGGAGCTCTGCGGGGGCCTCTGGCGG  
 5 CTGGTCCTGGCACAGCGCTGGATGGAGCGGCTCAAGACTGTCGCTGGGTC  
 CAAGATGCAAGGCTTGCTGGAGCGCGTGAACACGGAGATACACTTTGTCA  
 CCAAATGTGCCTTTCAGCCCCCCCCCAGCTGTCTTCGCTTCGTCCAGACC  
 AACATCTCCCGCCTCCTGCAGGAGACCTCCGAGCAGCTGGTGGCGCTGAA  
 GCCCTGGATCACTCGCCAGAACTTCTCCCGGTGCCTGGAGCTGCAGTGTG  
 10 AGCCCCGACTCCTCAACCCTG SEQ ID NO:110;

pMON32341.seq

15 GCCACTCAGGACTGTTCTTTCCAACACAGCCCCATCTCCTCCGACTTCGC  
 TGTCAAAATCCGTGAGCTGTCTGACTACCTGCTTCAAGATTACCCAGTCA  
 CCGTGGCCTCCAACCTGCAGGACGAGGAGCTCTGCGGGGGCCTCTGGCGG  
 CTGGTCCTGGCACAGCGCTGGATGGAGCGGCTCAAGACTGTCGCTGGGTC  
 CAAGATGCAAGGCTTGCTGGAGCGCGTGAACACGGAGATACACTTTGTCA  
 20 CCAAATGTGCCTTTCAGCCCCCCCCCAGCTGTCTTCGCTTCGTCCAGACC  
 AACATCTCCCGCCTCCTGCAGGAGACCTCCGAGCAGCTGGTGGCGCTGAA  
 GCCCTGGATCACTCGCCAGAACTTCTCCCGGTGCCTGGAGCTGCAGTGTG  
 AGCCC SEQ ID NO:111;

25 pMON32342.seq

GCCACTCAGGACTGCTCTTTTCAACACAGCCCCATCTCCTCCGACTTCGC  
 TGTCAAAATCCGTGAGCTGTCTGACTACCTGCTTCAAGATTACCCAGTCA  
 CCGTGGCCTCCAACCTGCAGGACGAGGAGCTCTGCGGGGGCCTCTGGCGG  
 30 CTGGTCCTGGCACAGCGCTGGATGGAGCGGCTCAAGACTGTCGCTGGGTC  
 CAAGATGCAAGGCTTGCTGGAGCGCGTGAACACGGAGATACACTTTGTCA  
 CCAAATGTGCCTTTCAGCCCCCCCCCAGCTGTCTTCGCTTCGTCCAGACC  
 AACATCTCCCGCCTCCTGCAGGAGACCTCCGAGCAGCTGGTGGCGCTGAA  
 GCCCTGGATCACTCGCCAGAACTTCTCCCGGTGCCTGGAGCTGCAGTGTG  
 35 AGCCCCGACTCCTCAACCCTG SEQ ID NO:112;

pMON32320.seq

40 GCCGACGAGGAGCTCTGCGGGGGCCTCTGGCGGCTGGTCCTGGCACAGCG  
 CTGGATGGAGCGGCTCAAGACTGTCGCTGGGTCCAAGATGCAAGGCTTGC  
 TGGAGCGCGTGAACACGGAGATACACTTTGTCAACCAAATGTGCCTTTCAG  
 CCCCCCCCCAGCTGTCTTCGCTTCGTCCAGACCAACATCTCCCGCCTCCT  
 GCAGGAGACCTCCGAGCAGCTGGTGGCGCTGAAGCCCTGGATCACTCGCC  
 45 AGAACTTCTCCCGGTGCCTGGAGCTGCAGTGTGAGCCCGACTCCTCAACC  
 CTGTCTGGAGGTAACGGATCCGGTGGCAATGGGAGCGGCGGAAATGGAAC  
 CCAGGACTGCTCCTTCCAACACAGCCCCATCTCCTCCGACTTCGTGTCA  
 AAATCCGTGAGCTGTCTGACTACCTGCTTCAAGATTACCCAGTCACCGTG  
 GCCTCCAACCTGCAG SEQ ID NO:113;

50

pMON32321.seq

GCCGACGAGGAGCTCTGCGGGGGCCTCTGGCGGCTGGTCCTGGCACAGCG  
 CTGGATGGAGCGGCTCAAGACTGTCGCTGGGTCCAAGATGCAAGGCTTGC  
 55 TGGAGCGCGTGAACACGGAGATACACTTTGTCAACCAAATGTGCCTTTCAG  
 CCCCCCCCCAGCTGTCTTCGCTTCGTCCAGACCAACATCTCCCGCCTCCT

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GCAGGAGACCTCCGAGCAGCTGGTGGCGCTGAAGCCCTGGATCACTCGCC  
 AGAACTTCTCCCGGTGCCTGGAGCTGCAGTGTGAGCCGACTCCTCAACC  
 CTGTGAGGCGGTAAACGGCAGTGGAGGTAATGGCAGCCAGGACTGCTCCTT  
 CCAACACAGCCCCATCTCCTCCGACTTCGCTGTCAAAATCCGTGAGCTGT  
 5 CTGACTACCTGCTTCAAGATTACCCAGTCACCGTGGCCTCCAACCTGCAG  
 SEQ ID NO:114;

pMON32322.seq

10 GCCGACGAGGAGCTCTGCGGGGGCCTCTGGCGGCTGGTCCTGGCACAGCG  
 CTGGATGGAGCGGCTCAAGACTGTGCTGGGTCCAAGATGCAAGGCTTGC  
 TGGAGCGCGTGAACACGGAGATACACTTTGTACCAAATGTGCCTTTTCAG  
 CCCCCCCCAGCTGTCTTCGCTTCGTCCAGACCAACATCTCCCGCCTCCT  
 GCAGGAGACCTCCGAGCAGCTGGTGGCGCTGAAGCCCTGGATCACTCGCC  
 15 AGAACTTCTCCCGGTGCCTGGAGCTGCAGTGTGAGCCGACTCCTCAACC  
 CTGTCTGGCGGCAACGGCAGCCAGGACTGCTCCTTCCAACACAGCCCCAT  
 CTCTCCGACTTCGCTGTCAAAATCCGTGAGCTGTCTGACTACCTGCTTC  
 AAGATTACCCAGTCACCGTGGCCTCCAACCTGCAG SEQ ID NO:115;

20

pMON32323.seq

GCCTCCAAGATGCAAGGCTTGCTGGAGCGCGTGAACACGGAGATACACTT  
 TGTACCAAATGTGCCTTTTCAGCCCCCCCCAGCTGTCTTCGCTTCGTCC  
 25 AGACCAACATCTCCCGCCTCCTGCAGGAGACCTCCGAGCAGCTGGTGGCG  
 CTGAAGCCCTGGATCACTCGCCAGAACTTCTCCCGGTGCCTGGAGCTGCA  
 GTGTGAGCCCGACTCCTCAACCTGTCTGGAGGTAACGGATCCGGTGGCA  
 ATGGGAGCGGCGAAATGGAACCCAGGACTGCTCCTTCCAACACAGCCCC  
 ATCTCCTCCGACTTCGCTGTCAAAATCCGTGAGCTGTCTGACTACCTGCT  
 30 TCAAGATTACCCAGTCACCGTGGCCTCCAACCTGCAGGACGAGGAGCTCT  
 GCGGGGGCCTCTGGCGGCTGGTCCTGGCACAGCGCTGGATGGAGCGGCTC  
 AAGACTGTCGCTGGG SEQ ID NO:116;

35

pMON32324.seq

GCCTCCAAGATGCAAGGCTTGCTGGAGCGCGTGAACACGGAGATACACTT  
 TGTACCAAATGTGCCTTTTCAGCCCCCCCCAGCTGTCTTCGCTTCGTCC  
 AGACCAACATCTCCCGCCTCCTGCAGGAGACCTCCGAGCAGCTGGTGGCG  
 40 CTGAAGCCCTGGATCACTCGCCAGAACTTCTCCCGGTGCCTGGAGCTGCA  
 GTGTGAGCCCGACTCCTCAACCTGTCTGGAGGTAACGGATCCGGAGGTA  
 ATGGCACCCAGGACTGCTCCTTCCAACACAGCCCCATCTCCTCCGACTTC  
 GCTGTCAAAATCCGTGAGCTGTCTGACTACCTGCTTCAAGATTACCCAGT  
 CACCGTGGCCTCCAACCTGCAGGACGAGGAGCTCTGCGGGGGCCTCTGGC  
 45 GGCTGGTCCTGGCACAGCGCTGGATGGAGCGGCTCAAGACTGTCGCTGGG  
 SEQ ID NO:117;

pMON32325.seq

50 GCCTCCAAGATGCAAGGCTTGCTGGAGCGCGTGAACACGGAGATACACTT  
 TGTACCAAATGTGCCTTTTCAGCCCCCCCCAGCTGTCTTCGCTTCGTCC  
 AGACCAACATCTCCCGCCTCCTGCAGGAGACCTCCGAGCAGCTGGTGGCG  
 CTGAAGCCCTGGATCACTCGCCAGAACTTCTCCCGGTGCCTGGAGCTGCA  
 GTGTGAGCCCGACTCCTCAACCTGTCTGGCGGCAACGGCACGCAGGACT  
 55 GCTCCTTCCAACACAGCCCCATCTCCTCCGACTTCGCTGTCAAAATCCGT  
 GAGCTGTCTGACTACCTGCTTCAAGATTACCCAGTCACCGTGGCCTCCA

CCTGCAGGACGAGGAGCTCTGCGGGGGCCTCTGGCGGCTGGTCCTGGCAC  
AGCGCTGGATGGAGCGGCTCAAGACTGTCGCTGGG SEQ ID NO:118;

5 pMON32326.seq

10 GCCCCCCCCAGCTGTCTTCGCTTCGTCCAGACCAACATCTCCCGCCTCCT  
GCAGGAGACCTCCGAGCAGCTGGTGGCGCTGAAGCCCTGGATCACTCGCC  
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CTGTCTGGAGGTAACGGCAGTGGTGGCAATGGGAGCGGTGGAAATGGAAC  
CCAGGACTGCTCCTTCCAACACAGCCCCATCTCCTCCGACTTCGCTGTCA  
AAATCCGTGAGCTGTCTGACTACCTGCTTCAAGATTACCCAGTCACCGTG  
GCCTCCAACCTGCAGGACGAGGAGCTCTGCGGGGGCCTCTGGCGGCTGGT  
15 CCTGGCACAGCGCTGGATGGAGCGGCTCAAGACTGTCGCTGGGTCCAAGA  
TGCAAGGCTTGCTGGAGCGCGTGAACACGGAGATACACTTTGTCACCAAA  
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pMON32327.seq

20 GCCCCCCCCAGCTGTCTTCGCTTCGTCCAGACCAACATCTCCCGCCTCCT  
GCAGGAGACCTCCGAGCAGCTGGTGGCGCTGAAGCCCTGGATCACTCGCC  
AGAACTTCTCCCGGTGCCTGGAGCTGCAGTGTGAGCCCGACTCCTCAACC  
CTGTGAGGCGGTAACGGCAGTGGAGGTAATGGCACCCAGGACTGCTCCTT  
25 CCAACACAGCCCCATCTCCTCCGACTTCGCTGTCAAAATCCGTGAGCTGT  
CTGACTACCTGCTTCAAGATTACCCAGTCACCGTGGCCTCCAACCTGCAG  
GACGAGGAGCTCTGCGGGGGCCTCTGGCGGCTGGTCCCTGGCACAGCGCTG  
GATGGAGCGGCTCAAGACTGTCGCTGGGTCCAAGATGCAAGGCTTGCTGG  
AGCGCGTGAACACGGAGATACACTTTGTCACCAAATGTGCCTTTCAGCCC  
30 SEQ ID NO:120;

pMON32328.seq

35 GCCCCCCCCAGCTGTCTTCGCTTCGTCCAGACCAACATCTCCCGCCTCCT  
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AGAACTTCTCCCGGTGCCTGGAGCTGCAGTGTGAGCCCGACTCCTCAACC  
CTGTCTGGCGGCAACGGCACGCAGGACTGCTCCTTCCAACACAGCCCCAT  
CTCCTCCGACTTCGCTGTCAAAATCCGTGAGCTGTCTGACTACCTGCTTC  
AAGATTACCCAGTCACCGTGGCCTCCAACCTGCAGGACGAGGAGCTCTGC  
40 GGGGGCCTCTGGCGGCTGGTCCCTGGCACAGCGCTGGATGGAGCGGCTCAA  
GACTGTGCTGGGTCCAAGATGCAAGGCTTGCTGGAGCGCGTGAACACGG  
AGATACACTTTGTCACCAAATGTGCCTTTCAGCCC SEQ ID NO:121;

45 pMON32348.seq

50 GCCGACGAGGAGCTCTGCGGGGGCCTCTGGCGGCTGGTCCTGGCACAGCG  
CTGGATGGAGCGGCTCAAGACTGTCGCTGGGTCCAAGATGCAAGGCTTGC  
TGGAGCGCGTGAACACGGAGATACACTTTGTCACCAAATGTGCCTTTCAG  
CCCCCCCCCAGCTGTCTTCGCTTCGTCCAGACCAACATCTCCCGCCTCCT  
GCAGGAGACCTCCGAGCAGCTGGTGGCGCTGAAGCCCTGGATCACTCGCC  
AGAACTTCTCCCGGTGCCTGGAGCTGCAGTGTGAGCCCGACTCCTCAACC  
CTGTCTGGAGGTAGTGGATCCGGAGGTTCTGGCAACCCAGGACTGCTCCT  
TCCAACACAGCCCCATCTCCTCCGACTTCGCTGTCAAAATCCGTGAGCTG  
55 TCTGACTACCTGCTTCAAGATTACCCAGTCACCGTGGCCTCCAACCTGCA  
G SEQ ID NO:122;

pMON32350.seq

5 GCCGACGAGGAGCTCTGCGGGGGCCTCTGGCGGCTGGTCCTGGCACAGCG  
CTGGATGGAGCGGCTCAAGACTGTCGCTGGGTCCAAGATGCAAGGCTTGC  
TGGAGCGCGTGAACACGGAGATACACTTTGTACCAAATGTGCCTTTTCAG  
CCCCCCCCCAGCTGTCTTCGCTTCGTCCAGACCAACATCTCCCGCCTCCT  
GCAGGAGACCTCCGAGCAGCTGGTGGCGCTGAAGCCCTGGATCACTCGCC  
10 AGAACTTCTCCCGGTGCCTGGAGCTGCAGTGTGAGCCGACTCCTCAACC  
CTGTCTGGAGGTAGTGGATCCGGTGGCAGTGGGAGCGGCGGATCTGGAAC  
CCAGGACTGCTCCTTCCAACACAGCCCCATCTCCTCCGACTTCGCTGTCA  
AAATCCGTGAGCTGTCTGACTACCTGCTTCAAGATTACCCAGTCACCGTG  
GCCTCCAACCTGCAG SEQ ID NO:123;

15

FLT3N.seq

CCATGGCCACCCAGGACTGCTCCTTCCAACACAGCCCCATCTCCTCCGAC  
20 TTCGCTGTCAAAATCCGTGAGCTGTCTGACTACCTGCTTCAAGATTACCC  
AGTCACCGTGGCCTCCAACCTGCAGGACGAGGAGCTCTGCGGGGGCCTCT  
GGCGGCTGGTCCTGGCACAGCGCTGGATGGAGCGGCTCAAGACTGTCGCT  
GGGTCCAAGATGCAAGGCTTGCTGGAGCGCGTGAACACGGAGATACACTT  
TGTCACCAAATGTGCCTTTTCAGCCCCCCCCCAGCTGTCTTCGCTTCGTCC  
25 AGACCAACATCTCCCGCCTCCTGCAGGAGACCTCCGAGCAGCTGGTGGCG  
CTGAAGCCCTGGATCACTCGCCAGAACTTCTCCCGGTGCCTGGAGCTGCA  
GTGTGAGCCCGACTCCTCAACCCTGGGCGGTGGATCC SEQ ID NO:124;

30 FLT3C.seq

GGATCCGGAGGTACCCAGGACTGCTCCTTCCAACACAGCCCCATCTCCTC  
CGACTTCGCTGTCAAAATCCGTGAGCTGTCTGACTACCTGCTTCAAGATT  
ACCCAGTCACCGTGGCCTCCAACCTGCAGGACGAGGAGCTCTGCGGGGGC  
35 CTCTGGCGGCTGGTCCTGGCACAGCGCTGGATGGAGCGGCTCAAGACTGT  
CGCTGGGTCCAAGATGCAAGGCTTGCTGGAGCGCGTGAACACGGAGATAC  
ACTTTGTACCAAATGTGCCTTTTCAGCCCCCCCCCAGCTGTCTTCGCTTC  
GTCCAGACCAACATCTCCCGCCTCCTGCAGGAGACCTCCGAGCAGCTGGT  
GGCGCTGAAGCCCTGGATCACTCGCCAGAACTTCTCCCGGTGCCTGGAGC  
40 TGCAGTGTGAGCCCGACTCCTCAACCCTGTAAGCTT SEQ ID NO:125;

FLT7N.seq

45 CCATGGCCACCCAGGACTGCTCCTTCCAACACAGCCCCATCTCCTCCGAC  
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AGTCACCGTGGCCTCCAACCTGCAGGACGAGGAGCTCTGCGGGGGCCTCT  
GGCGGCTGGTCCTGGCACAGCGCTGGATGGAGCGGCTCAAGACTGTCGCT  
GGGTCCAAGATGCAAGGCTTGCTGGAGCGCGTGAACACGGAGATACACTT  
50 TGTCACCAAATGTGCCTTTTCAGCCCCCCCCCAGCTGTCTTCGCTTCGTCC  
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SEQ ID NO:126;

55

FLT4C.seq

GGATCCGGAGGTGGCACCCAGGACTGCTCCTTCCAACACAGCCCCATCTC  
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ATTACCCAGTCACCGTGGCCTCCAACCTGCAGGACGAGGAGCTCTGCGGG  
5 GGCCTCTGGCGGCTGGTCCTGGCACAGCGCTGGATGGAGCGGCTCAAGAC  
TGTCGCTGGGTCCAAGATGCAAGGCTTGCTGGAGCGCGTGAACACGGAGA  
TACACTTTGTACCAAATGTGCCTTTCAGCCCCCCCCCAGCTGTCTTCGC  
TTCGTCCAGACCAACATCTCCCGCCTCCTGCAGGAGACCTCCGAGCAGCT  
GGTGGCGCTGAAGCCCTGGATCACTCGCCAGAACTTCTCCCGGTGCCTGG  
10 AGCTGCAGTGTACCCCGACTCCTCAACCCTGTAAGCTT SEQ ID NO:127;

## FLT11N.seq

15 CCATGGCCACCCAGGACTGCTCCTTCCAACACAGCCCCATCTCCTCCGAC  
TTCGCTGTCAAAATCCGTGAGCTGTCTGACTACCTGCTTCAAGATTACCC  
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GGCGGCTGGTCCTGGCACAGCGCTGGATGGAGCGGCTCAAGACTGTGCT  
GGGTCCAAGATGCAAGGCTTGCTGGAGCGCGTGAACACGGAGATACACTT  
20 TGTACCAAATGTGCCTTTCAGCCCCCCCCCAGCTGTCTTCGCTTCGTCC  
AGACCAACATCTCCCGCCTCCTGCAGGAGACCTCCGAGCAGCTGGTGGCG  
CTGAAGCCCTGGATCACTCGCCAGAACTTCTCCCGGTGCCTGGAGCTGCA  
GTGTCAGCCCGACTCCTCAACCCTGGGCGGTGGGTGAGGAGGTGGGTCAG  
GAGGTGGATCC SEQ ID NO:128;

## 25 FLT10C.seq

GGATCCGGAGGTGGCTCAGGGGGAGGTAGTGGTACCCAGGACTGCTCCTT  
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30 CTGACTACCTGCTTCAAGATTACCCAGTCACCGTGGCCTCCAACCTGCAG  
GACGAGGAGCTCTGCGGGGGCCTCTGGCGGCTGGTCCTGGCACAGCGCTG  
GATGGAGCGGCTCAAGACTGTGCTGGGTCCAAGATGCAAGGCTTGCTGG  
AGCGCGTGAACACGGAGATACACTTTGTACCAAATGTGCCTTTCAGCCC  
CCCCCAGCTGTCTTCGCTTCGTCCAGACCAACATCTCCCGCCTCCTGCA  
35 GGAGACCTCCGAGCAGCTGGTGGCGCTGAAGCCCTGGATCACTCGCCAGA  
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TAAGCTT SEQ ID NO:129;

## 40 pMON32365.seq

GCCGACGAGGAGCTCTGCGGGGGCCTCTGGCGGCTGGTCCTGGCACAGCG  
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TGGAGCGCGTGAACACGGAGATACACTTTGTACCAAATGTGCCTTTCAG  
45 CCCCCCCCCAGCTGTCTTCGCTTCGTCCAGACCAACATCTCCCGCCTCCT  
GCAGGAGACCTCCGAGCAGCTGGTGGCGCTGAAGCCCTGGATCACTCGCC  
AGAACTTCTCCCGGTGCCTGGAGCTGCAGTGTGAGCCCGACTCCTCAACC  
CTGGGCGGTGGATCCGGAGGTACCCAGGACTGCTCCTTCCAACACAGCCC  
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50 TTCAAGATTACCCAGTCACCGTGGCCTCCAACCTGCAG SEQ ID NO:130;

## pMON32366.seq

55 GCCGACGAGGAGCTCTGCGGGGGCCTCTGGCGGCTGGTCCTGGCACAGCG  
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TGGAGCGCGTGAACACGGAGATACACTTTGTACCAAATGTGCCTTTTCAG  
CCCCCCCCCAGCTGTCTTCGCTTCGTCCAGACCAACATCTCCCGCCTCCT  
GCAGGAGACCTCCGAGCAGCTGGTGGCGCTGAAGCCCTGGATCACTCGCC  
AGAAGTTCTCCCGGTGCCTGGAGCTGCAGTGTGAGCCCGACTCCTCAACC  
5 CTGGGCGGTGGATCCGGAGGTGGCACCCAGGACTGCTCCTTCCAACACAG  
CCCCATCTCCTCCGACTTCGCTGTCAAAATCCGTGAGCTGTCTGACTACC  
TGCTTCAAGATTACCCAGTCACCGTGGCCTCCAACCTGCAG SEQ ID NO:131;

10 pMON32367.seq

GGCGACGAGGAGCTCTGCGGGGGCCTCTGGCGGCTGGTCTTGGCACAGCG  
CTGGATGGAGCGGCTCAAGACTGTGCTGGGTCCAAGATGCAAGGCTTGC  
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15 CCCCCCCCCAGCTGTCTTCGCTTCGTCCAGACCAACATCTCCCGCCTCCT  
GCAGGAGACCTCCGAGCAGCTGGTGGCGCTGAAGCCCTGGATCACTCGCC  
AGAAGTTCTCCCGGTGCCTGGAGCTGCAGTGTGAGCCCGACTCCTCAACC  
CTGGGCGGTGGGTGAGGAGGTGGATCCGGAGGTACCCAGGACTGCTCCTT  
CCAACACAGCCCCATCTCCTCCGACTTCGCTGTCAAAATCCGTGAGCTGT  
20 CTGACTACCTGCTTCAAGATTACCCAGTCACCGTGGCCTCCAACCTGCAG  
SEQ ID NO:132;

pMON32368.seq

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CCCCCCCCCAGCTGTCTTCGCTTCGTCCAGACCAACATCTCCCGCCTCCT  
GCAGGAGACCTCCGAGCAGCTGGTGGCGCTGAAGCCCTGGATCACTCGCC  
30 AGAAGTTCTCCCGGTGCCTGGAGCTGCAGTGTGAGCCCGACTCCTCAACC  
CTGGGCGGTGGATCCGGAGGTGGCTCAGGGGGAGGTAGTGGTACCCAGGA  
CTGCTCCTTCCAACACAGCCCCATCTCCTCCGACTTCGCTGTCAAAATCC  
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AACCTGCAG SEQ ID NO:133;

35

pMON32369.seq

GGCGACGAGGAGCTCTGCGGGGGCCTCTGGCGGCTGGTCTTGGCACAGCG  
40 CTGGATGGAGCGGCTCAAGACTGTGCTGGGTCCAAGATGCAAGGCTTGC  
TGGAGCGCGTGAACACGGAGATACACTTTGTACCAAATGTGCCTTTTCAG  
CCCCCCCCCAGCTGTCTTCGCTTCGTCCAGACCAACATCTCCCGCCTCCT  
GCAGGAGACCTCCGAGCAGCTGGTGGCGCTGAAGCCCTGGATCACTCGCC  
AGAAGTTCTCCCGGTGCCTGGAGCTGCAGTGTGAGCCCGACTCCTCAACC  
45 CTGGGCGGTGGGTGAGGAGGTGGGTGAGGAGGTGGATCCGGAGGTGGCAC  
CCAGGACTGCTCCTTCCAACACAGCCCCATCTCCTCCGACTTCGCTGTCA  
AAATCCGTGAGCTGTCTGACTACCTGCTTCAAGATTACCCAGTCACCGTG  
GCCTCCAACCTGCAG SEQ ID NO:134;

50 pMON32370.seq

GGCGACGAGGAGCTCTGCGGGGGCCTCTGGCGGCTGGTCTTGGCACAGCG  
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55 CCCCCCCCCAGCTGCCTTCGCTTCGTCCAGACCAACATCTCCCGCCTCCT  
GCAGGAGACCTCCGAGCAGCTGGTGGCGCTGAAGCCCTGGATCACTCGCC

AGAACTTCTCCCGGTGCCTGGAGCTGCAGTGTGAGCCCGACTCCTCAACC  
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AGGGGAGGTAGTGGTACCCAGGACTGCTCCTTCCAACACAGCCCCATCT  
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5 GATTACCCAGTCACCGTGGCCTCCAACCTGCAG SEQ ID NO:135;

pMON35712.seq

10 GCCGATTACCCAGTCACCGTGGCCTCCAACCTGCAGGACGAGGAGCTCTGCGGGG  
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ACCAAATGTGCCTTTCAGCCCCCCCCCAGCTGTCTTCGCTTCGTCCAGACCAACA  
TCTCCCGCTCCTGCAGGAGACCTCCGAGCAGCTGGTGGCGCTGAAGCCCTGGAT  
CACTCGCCAGAACTTCTCCCGGTGCCTGGAGCTGCAGTGTGAGCCCGACTCCTCA  
15 ACCCTGGCGGTGGGTGAGGAGGTGGGTGAGGAGGTGGATCCGGAGGTGGCACCC  
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TGAGCTGTCTGACTACCTGCTTCAA SEQ ID NO:136;

pMON35713.seq

20 GCCGCCTCCAACCTGCAGGACGAGGAGCTCTGCGGGGGCCTCTGGCGGCTGGTCC  
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CCCCCCCCCAGCTGTCTTCGCTTCGTCCAGACCAACATCTCCCGCTCCTGCAGG  
25 AGACCTCCGAGCAGCTGGTGGCGCTGAAGCCCTGGATCACTCGCCAGAACTTCTC  
CCGCTGCCTGGAGCTGCAGTGTGAGCCCGACTCCTCAACCCTGGGCGGTGGGTCA  
GGAGGTGGGTGAGGAGGTGGATCCGGAGGTGGCACCCAGGACTGCTCCTTCCAAC  
ACAGCCCCATCTCCTCCGACTTCGCTGTCAAAATCCGTGAGCTGTCTGACTACCT  
GCTTCAAGATTACCCAGTCACCGTG SEQ ID NO:137;

30 pMON35714.seq

GCCGCTCGCTGGGTCCAAGATGCAAGGCTTGTCTGGAGCGCGTGAACACGGAGATAC  
ACTTTGTACCAAATGTGCCTTTCAGCCCCCCCCCAGCTGTCTTCGCTTCGTCCA  
35 GACCAACATCTCCCGCTCCTGCAGGAGACCTCCGAGCAGCTGGTGGCGCTGAAG  
CCCTGGATCACTCGCCAGAACTTCTCCCGGTGCCTGGAGCTGCAGTGTGAGCCCG  
ACTCCTCAACCCTGGGCGGTGGGTGAGGAGGTGGGTGAGGAGGTGGATCCGGAGG  
TGGCACCCAGGACTGCTCCTTCCAACACAGCCCCATCTCCTCCGACTTCGCTGTC  
AAAATCCGTGAGCTGTCTGACTACCTGCTTCAAGATTACCCAGTCACCGTGGCCT  
40 CCAACCTGCAGGACGAGGAGCTCTGCGGGGGCCTCTGGCGGCTGGTCTTGGCACA  
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pMON35715.seq

45 GCCTCCAAGATGCAAGGCTTGTCTGGAGCGCGTGAACACGGAGATACACTTTGTCA  
CCAAATGTGCCTTTCAGCCCCCCCCCAGCTGTCTTCGCTTCGTCCAGACCAACAT  
CTCCCGCTCCTGCAGGAGACCTCCGAGCAGCTGGTGGCGCTGAAGCCCTGGATC  
ACTCGCCAGAACTTCTCCCGGTGCCTGGAGCTGCAGTGTGAGCCCGACTCCTCAA  
CCCTGGGCGGTGGGTGAGGAGGTGGGTGAGGAGGTGGATCCGGAGGTGGCACCCA  
50 GGACTGCTCCTTCCAACACAGCCCCATCTCCTCCGACTTCGCTGTCAAAATCCGT  
GAGCTGTCTGACTACCTGCTTCAAGATTACCCAGTCACCGTGGCCTCCAACCTGC  
AGGACGAGGAGCTCTGCGGGGGCCTCTGGCGGCTGGTCTTGGCACAGCGCTGGAT  
GGAGCGGCTCAAGACTGTGCTGGG SEQ ID NO:139;

55 pMON35716.seq

5 GCCCCCCCCAGCTGTCTTCGCTTCGTCCAGACCAACATCTCCCGCCTCCTGCAGG  
AGACCTCCGAGCAGCTGGTGGCGCTGAAGCCCTGGATCACTCGCCAGAACTTCTC  
CCGGTGCCTGGAGCTGCAGTGTACGCCGACTCCTCAACCCTGGGCGGTGGGTCA  
GGAGGTGGGTGAGGAGGTGGATCCGGAGGTGGCACCCAGGACTGCTCCTTCCAAC  
10 ACAGCCCCATCTCCTCCGACTTCGCTGTCAAAATCCGTGAGCTGTCTGACTACCT  
GCTTCAAGATTACCCAGTCACCGTGGCCTCCAACCTGCAGGACGAGGAGCTCTGC  
GGGGGCCTCTGGCGGCTGGTCCTGGCACAGCGCTGGATGGAGCGGCTCAAGACTG  
TCGCTGGGTCCAAGATGCAAGGCTTGCTGGAGCGCGTGAACACGGAGATACACTT  
TGTCACCAAATGTGCCTTTTCAGCCC SEQ ID NO:140;

10 pMON 35717.seq

15 GCCCGCTTCGTCCAGACCAACATCTCCCGCCTCCTGCAGGAGACCTCCGAGCAGC  
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GCAGTGTACGCCGACTCCTCAACCCTGGGCGGTGGGTGAGGAGGTGGGTGAGG  
GGTGGATCCGGAGGTGGCACCCAGGACTGCTCCTTCCAACACAGCCCCATCTCCT  
CCGACTTCGCTGTCAAAATCCGTGAGCTGTCTGACTACCTGCTTCAAGATTACCC  
AGTCACCGTGGCCTCCAACCTGCAGGACGAGGAGCTCTGCGGGGGCCTCTGGCGG  
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20 TGCAAGGCTTGCTGGAGCGCGTGAACACGGAGATACACTTTGTACCAAATGTGC  
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pMON 35718.seq

25 GCCACCAACATCTCCCGCCTCCTGCAGGAGACCTCCGAGCAGCTGGTGGCGCTGA  
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CGACTCCTCAACCCTGGGCGGTGGGTGAGGAGGTGGGTGAGGAGGTGGATCCGGA  
GGTGGCACCCAGGACTGCTCCTTCCAACACAGCCCCATCTCCTCCGACTTCGCTG  
TCAAAATCCGTGAGCTGTCTGACTACCTGCTTCAAGATTACCCAGTCACCGTGGC  
30 CTCCAACCTGCAGGACGAGGAGCTCTGCGGGGGCCTCTGGCGGCTGGTCCTGGCA  
CAGCGCTGGATGGAGCGGCTCAAGACTGTCGCTGGGTCCAAGATGCAAGGCTTGC  
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CCCCAGCTGTCTTCGCTTCGTCCAG SEQ ID NO:143;

TABLE 3  
PROTEIN SEQUENCES

- 5 pMON30237.pep
- AlaThrGlnAspCysSerPheGlnHisSerProIleSerSerAspPheAlaValLysIle  
ArgGluLeuSerAspTyrLeuLeuGlnAspTyrProValThrValAlaSerAsnLeuGln  
AspGluGluLeuCysGlyAlaLeuTrpArgLeuValLeuAlaGlnArgTrpMetGluArg  
10 LeuLysThrValAlaGlySerLysMetGlnGlyLeuLeuGluArgValAsnThrGluIle  
HisPheValThrLysCysAlaPheGlnProProProSerCysLeuArgPheValGlnThr  
AsnIleSerArgLeuLeuGlnGluThrSerGluGlnLeuValAlaLeuLysProTrpIle  
ThrArgGlnAsnPheSerArgCysLeuGluLeuGlnCysGlnPro SEQ ID NO:1;
- 15 pMON30238.pep
- AlaThrGlnAspCysSerPheGlnHisSerProIleSerSerAspPheAlaValLysIle  
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20 AspGluGluLeuCysGlyGlyLeuTrpArgLeuValLeuAlaGlnArgTrpMetGluArg  
LeuLysThrValAlaGlySerLysMetGlnGlyLeuLeuGluArgValAsnThrGluIle  
HisPheValThrLysCysAlaPheGlnProProProSerCysLeuArgPheValGlnThr  
AsnIleSerArgLeuLeuGlnGluThrSerGluGlnLeuValAlaLeuLysProTrpIle  
ThrArgGlnAsnPheSerArgCysLeuGluLeuGlnCysGlnPro AspSerSerThrLeu  
25 SEQ ID NO:2;
- pMON30239.pep
- AlaThrGlnAspCysSerPheGlnHisSerProIleSerSerAspPheAlaValLysIle  
30 ArgGluLeuSerAspTyrLeuLeuGlnAspTyrProValThrValAlaSerAsnLeuGln  
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HisPheValThrLysCysAlaPheGlnGluThrSerGluGlnLeuValAlaLeuLysPro  
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35 ThrLeu SEQ ID NO:3;
- pMON32329.pep
- 40 GlyThrGlnAspCysSerPheGlnHisSerProIleSerSerAspPheAlaValLysIle  
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AspGluGluLeuCysGlyGlyLeuTrpArgLeuValLeuAlaGlnArgTrpMetGluArg  
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45 AsnIleSerArgLeuLeuGlnGluThrSerGluGlnLeuValAlaLeuLysProTrpIle  
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- pMON32330.pep
- 50 GlyThrGlnAspCysSerPheGlnHisSerProIleSerSerAspPheAlaValLysIle  
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AspGluGluLeuCysGlyGlyLeuTrpArgLeuValLeuAlaGlnArgTrpMetGluArg  
LeuLysThrValAlaGlySerLysMetGlnGlyLeuLeuGluArgValAsnThrGluIle  
55 HisPheValThrLysCysAlaPheGlnProProProSerCysLeuArgPheValGlnThr

AsnIleSerArgLeuLeuGlnGluThrSerGluGlnLeuValAlaLeuLysProTrpIle  
ThrArgGlnAsnPheSerArgCysLeuGluLeuGlnCysGlnProAspSerSerThrLeu  
SEQ ID NO:5;

5 pMON32341.pep

AlaThrGlnAspCysSerPheGlnHisSerProIleSerSerAspPheAlaValLysIle  
ArgGluLeuSerAspTyrLeuLeuGlnAspTyrProValThrValAlaSerAsnLeuGln  
AspGluGluLeuCysGlyGlyLeuTrpArgLeuValLeuAlaGlnArgTrpMetGluArg  
10 LeuLysThrValAlaGlySerLysMetGlnGlyLeuLeuGluArgValAsnThrGluIle  
HisPheValThrLysCysAlaPheGlnProProProSerCysLeuArgPheValGlnThr  
AsnIleSerArgLeuLeuGlnGluThrSerGluGlnLeuValAlaLeuLysProTrpIle  
ThrArgGlnAsnPheSerArgCysLeuGluLeuGlnCysGlnPro SEQ ID NO:6;

15 pMON32342.pep

AlaThrGlnAspCysSerPheGlnHisSerProIleSerSerAspPheAlaValLysIle  
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20 AspGluGluLeuCysGlyGlyLeuTrpArgLeuValLeuAlaGlnArgTrpMetGluArg  
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HisPheValThrLysCysAlaPheGlnProProProSerCysLeuArgPheValGlnThr  
AsnIleSerArgLeuLeuGlnGluThrSerGluGlnLeuValAlaLeuLysProTrpIle  
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25 SEQ ID NO:7;

pMON32320.pep

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30 ArgLeuLysThrValAlaGlySerLysMetGlnGlyLeuLeuGluArgValAsnThrGlu  
IleHisPheValThrLysCysAlaPheGlnProProProSerCysLeuArgPheValGln  
ThrAsnIleSerArgLeuLeuGlnGluThrSerGluGlnLeuValAlaLeuLysProTrp  
IleThrArgGlnAsnPheSerArgCysLeuGluLeuGlnCysGlnProAspSerSerThr  
LeuSerGlyGlyAsnGlySerGlyGlyAsnGlySerGlyGlyAsnGlyThrGlnAspCys  
35 SerPheGlnHisSerProIleSerSerAspPheAlaValLysIleArgGluLeuSerAsp  
TyrLeuLeuGlnAspTyrProValThrValAlaSerAsnLeuGln SEQ ID NO:8;

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40 AlaAspGluGluLeuCysGlyGlyLeuTrpArgLeuValLeuAlaGlnArgTrpMetGlu  
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IleHisPheValThrLysCysAlaPheGlnProProProSerCysLeuArgPheValGln  
ThrAsnIleSerArgLeuLeuGlnGluThrSerGluGlnLeuValAlaLeuLysProTrp  
45 IleThrArgGlnAsnPheSerArgCysLeuGluLeuGlnCysGlnProAspSerSerThr  
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TyrProValThrValAlaSerAsnLeuGln SEQ ID NO:9;

50 pMON32322.pep

AlaAspGluGluLeuCysGlyGlyLeuTrpArgLeuValLeuAlaGlnArgTrpMetGlu  
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55 IleHisPheValThrLysCysAlaPheGlnProProProSerCysLeuArgPheValGln  
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IleThrArgGlnAsnPheSerArgCysLeuGluLeuGlnCysGlnProAspSerSerThr  
 LeuSerGlyGlyAsnGlyThrGlnAspCysSerPheGlnHisSerProIleSerSerAsp  
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pMON32323.pep

AlaSerLysMetGlnGlyLeuLeuGluArgValAsnThrGluIleHisPheValThrLys  
 10 CysAlaPheGlnProProProSerCysLeuArgPheValGlnThrAsnIleSerArgLeu  
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 SerArgCysLeuGluLeuGlnCysGlnProAspSerSerThrLeuSerGlyGlyAsnGly  
 SerGlyGlyAsnGlySerGlyGlyAsnGlyThrGlnAspCysSerPheGlnHisSerPro  
 IleSerSerAspPheAlaValLysIleArgGluLeuSerAspTyrLeuLeuGlnAspTyr  
 15 ProValThrValAlaSerAsnLeuGlnAspGluGluLeuCysGlyGlyLeuTrpArgLeu  
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pMON32324.pep

20

AlaSerLysMetGlnGlyLeuLeuGluArgValAsnThrGluIleHisPheValThrLys  
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 LeuGlnGluThrSerGluGlnLeuValAlaLeuLysProTrpIleThrArgGlnAsnPhe  
 SerArgCysLeuGluLeuGlnCysGlnProAspSerSerThrLeuSerGlyGlyAsnGly  
 25 SerGlyGlyAsnGlyThrGlnAspCysSerPheGlnHisSerProIleSerSerAspPhe  
 AlaValLysIleArgGluLeuSerAspTyrLeuLeuGlnAspTyrProValThrValAla  
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 TrpMetGluArgLeuLysThrValAlaGly SEQ ID NO:12;

30

pMON32325.pep

AlaSerLysMetGlnGlyLeuLeuGluArgValAsnThrGluIleHisPheValThrLys  
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 35 LeuGlnGluThrSerGluGlnLeuValAlaLeuLysProTrpIleThrArgGlnAsnPhe  
 SerArgCysLeuGluLeuGlnCysGlnProAspSerSerThrLeuSerGlyGlyAsnGly  
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 GluLeuSerAspTyrLeuLeuGlnAspTyrProValThrValAlaSerAsnLeuGlnAsp  
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 40 LysThrValAlaGly SEQ ID NO:13;

pMON32326.pep

AlaProProSerCysLeuArgPheValGlnThrAsnIleSerArgLeuLeuGlnGluThr  
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 GluLeuGlnCysGlnProAspSerSerThrLeuSerGlyGlyAsnGlySerGlyGlyAsn  
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 50 AlaSerAsnLeuGlnAspGluGluLeuCysGlyGlyLeuTrpArgLeuValLeuAlaGln  
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55 pMON32327.pep

AlaProProSerCysLeuArgPheValGlnThrAsnIleSerArgLeuLeuGlnGluThr  
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 GluLeuGlnCysGlnProAspSerSerThrLeuSerGlyGlyAsnGlySerGlyGlyAsn  
 GlyThrGlnAspCysSerPheGlnHisSerProIleSerSerAspPheAlaValLysIle  
 5 ArgGluLeuSerAspTyrLeuLeuGlnAspTyrProValThrValAlaSerAsnLeuGln  
 AspGluGluLeuCysGlyGlyLeuTrpArgLeuValLeuAlaGlnArgTrpMetGluArg  
 LeuLysThrValAlaGlySerLysMetGlnGlyLeuLeuGluArgValAsnThrGluIle  
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pMON32328.pep

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 15 GluLeuGlnCysGlnProAspSerSerThrLeuSerGlyGlyAsnGlyThrGlnAspCys  
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 TyrLeuLeuGlnAspTyrProValThrValAlaSerAsnLeuGlnAspGluGluLeuCys  
 GlyGlyLeuTrpArgLeuValLeuAlaGlnArgTrpMetGluArgLeuLysThrValAla  
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 20 CysAlaPheGlnPro SEQ ID NO:16;

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 ThrAsnIleSerArgLeuLeuGlnGluThrSerGluGlnLeuValAlaLeuLysProTrp  
 IleThrArgGlnAsnPheSerArgCysLeuGluLeuGlnCysGlnProAspSerSerThr  
 30 LeuSerGlyGlySerGlySerGlyGlySerGlySerGlyGlySerGlyThrGlnAspCys  
 SerPheGlnHisSerProIleSerSerAspPheAlaValLysIleArgGluLeuSerAsp  
 TyrLeuLeuGlnAspTyrProValThrValAlaSerAsnLeuGln SEQ ID NO:17;

35 pMON32350.pep

AlaAspGluGluLeuCysGlyGlyLeuTrpArgLeuValLeuAlaGlnArgTrpMetGlu  
 ArgLeuLysThrValAlaGlySerLysMetGlnGlyLeuLeuGluArgValAsnThrGlu  
 IleHisPheValThrLysCysAlaPheGlnProProProSerCysLeuArgPheValGln  
 40 ThrAsnIleSerArgLeuLeuGlnGluThrSerGluGlnLeuValAlaLeuLysProTrp  
 IleThrArgGlnAsnPheSerArgCysLeuGluLeuGlnCysGlnProAspSerSerThr  
 LeuSerGlyGlySerGlySerGlyGlySerGlyThrGlnAspCysSerPheGlnHisSer  
 ProIleSerSerAspPheAlaValLysIleArgGluLeuSerAspTyrLeuLeuGlnAsp  
 TyrProValThrValAlaSerAsnLeuGln SEQ ID NO:18;

45

FLT3N.pep

MetAlaThrGlnAspCysSerPheGlnHisSerProIleSerSerAspPheAlaValLys  
 50 IleArgGluLeuSerAspTyrLeuLeuGlnAspTyrProValThrValAlaSerAsnLeu  
 GlnAspGluGluLeuCysGlyGlyLeuTrpArgLeuValLeuAlaGlnArgTrpMetGlu  
 ArgLeuLysThrValAlaGlySerLysMetGlnGlyLeuLeuGluArgValAsnThrGlu  
 IleHisPheValThrLysCysAlaPheGlnProProProSerCysLeuArgPheValGln  
 ThrAsnIleSerArgLeuLeuGlnGluThrSerGluGlnLeuValAlaLeuLysProTrp  
 55 IleThrArgGlnAsnPheSerArgCysLeuGluLeuGlnCysGlnProAspSerSerThr  
 LeuGlyGlyGlySer SEQ ID NO:19;

## FLT3C.pep

5 GlySerGlyGlyThrGlnAspCysSerPheGlnHisSerProIleSerSerAspPheAla  
ValLysIleArgGluLeuSerAspTyrLeuLeuGlnAspTyrProValThrValAlaSer  
AsnLeuGlnAspGluGluLeuCysGlyGlyLeuTrpArgLeuValLeuAlaGlnArgTrp  
MetGluArgLeuLysThrValAlaGlySerLysMetGlnGlyLeuLeuGluArgValAsn  
ThrGluIleHisPheValThrLysCysAlaPheGlnProProProSerCysLeuArgPhe  
10 ValGlnThrAsnIleSerArgLeuLeuGlnGluThrSerGluGlnLeuValAlaLeuLys  
ProTrpIleThrArgGlnAsnPheSerArgCysLeuGluLeuGlnCysGlnProAspSer  
SerThrLeu SEQ ID NO:20;

## 15 FLT7N.pep

MetAlaThrGlnAspCysSerPheGlnHisSerProIleSerSerAspPheAlaValLys  
IleArgGluLeuSerAspTyrLeuLeuGlnAspTyrProValThrValAlaSerAsnLeu  
GlnAspGluGluLeuCysGlyGlyLeuTrpArgLeuValLeuAlaGlnArgTrpMetGlu  
20 ArgLeuLysThrValAlaGlySerLysMetGlnGlyLeuLeuGluArgValAsnThrGlu  
IleHisPheValThrLysCysAlaPheGlnProProProSerCysLeuArgPheValGln  
ThrAsnIleSerArgLeuLeuGlnGluThrSerGluGlnLeuValAlaLeuLysProTrp  
IleThrArgGlnAsnPheSerArgCysLeuGluLeuGlnCysGlnProAspSerSerThr  
LeuGlyGlyGlySerGlyGlyGlySer SEQ ID NO:21;

25

## FLT4C.pep

GlySerGlyGlyGlyThrGlnAspCysSerPheGlnHisSerProIleSerSerAspPhe  
30 AlaValLysIleArgGluLeuSerAspTyrLeuLeuGlnAspTyrProValThrValAla  
SerAsnLeuGlnAspGluGluLeuCysGlyGlyLeuTrpArgLeuValLeuAlaGlnArg  
TrpMetGluArgLeuLysThrValAlaGlySerLysMetGlnGlyLeuLeuGluArgVal  
AsnThrGluIleHisPheValThrLysCysAlaPheGlnProProProSerCysLeuArg  
PheValGlnThrAsnIleSerArgLeuLeuGlnGluThrSerGluGlnLeuValAlaLeu  
35 LysProTrpIleThrArgGlnAsnPheSerArgCysLeuGluLeuGlnCysGlnProAsp  
SerSerThrLeu SEQ ID NO:22;

## FLT11N.pep

40

MetAlaThrGlnAspCysSerPheGlnHisSerProIleSerSerAspPheAlaValLys  
IleArgGluLeuSerAspTyrLeuLeuGlnAspTyrProValThrValAlaSerAsnLeu  
GlnAspGluGluLeuCysGlyGlyLeuTrpArgLeuValLeuAlaGlnArgTrpMetGlu  
ArgLeuLysThrValAlaGlySerLysMetGlnGlyLeuLeuGluArgValAsnThrGlu  
45 IleHisPheValThrLysCysAlaPheGlnProProProSerCysLeuArgPheValGln  
ThrAsnIleSerArgLeuLeuGlnGluThrSerGluGlnLeuValAlaLeuLysProTrp  
IleThrArgGlnAsnPheSerArgCysLeuGluLeuGlnCysGlnProAspSerSerThr  
LeuGlyGlyGlySerGlyGlyGlySer SEQ ID NO:23;

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## FLT10C.pep

GlySerGlyGlyGlySerGlyGlyGlySerGlyThrGlnAspCysSerPheGlnHisSer  
ProIleSerSerAspPheAlaValLysIleArgGluLeuSerAspTyrLeuLeuGlnAsp  
55 TyrProValThrValAlaSerAsnLeuGlnAspGluGluLeuCysGlyGlyLeuTrpArg  
LeuValLeuAlaGlnArgTrpMetGluArgLeuLysThrValAlaGlySerLysMetGln

5 GlyLeuLeuGluArgValAsnThrGluIleHisPheValThrLysCysAlaPheGlnPro  
ProProSerCysLeuArgPheValGlnThrAsnIleSerArgLeuLeuGlnGluThrSer  
GluGlnLeuValAlaLeuLysProTrpIleThrArgGlnAsnPheSerArgCysLeuGlu  
LeuGlnCysGlnProAspSerSerThrLeu SEQ ID NO:24;

pMON32365.pep

10 AlaAspGluGluLeuCysGlyGlyLeuTrpArgLeuValLeuAlaGlnArgTrpMetGlu  
ArgLeuLysThrValAlaGlySerLysMetGlnGlyLeuLeuGluArgValAsnThrGlu  
IleHisPheValThrLysCysAlaPheGlnProProProSerCysLeuArgPheValGln  
ThrAsnIleSerArgLeuLeuGlnGluThrSerGluGlnLeuValAlaLeuLysProTrp  
IleThrArgGlnAsnPheSerArgCysLeuGluLeuGlnCysGlnProAspSerSerThr  
15 LeuGlyGlyGlySerGlyGlyThrGlnAspCysSerPheGlnHisSerProIleSerSer  
AspPheAlaValLysIleArgGluLeuSerAspTyrLeuLeuGlnAspTyrProValThr  
ValAlaSerAsnLeuGln SEQ ID NO:25;

pMON32366.pep

20 AlaAspGluGluLeuCysGlyGlyLeuTrpArgLeuValLeuAlaGlnArgTrpMetGlu  
ArgLeuLysThrValAlaGlySerLysMetGlnGlyLeuLeuGluArgValAsnThrGlu  
IleHisPheValThrLysCysAlaPheGlnProProProSerCysLeuArgPheValGln  
ThrAsnIleSerArgLeuLeuGlnGluThrSerGluGlnLeuValAlaLeuLysProTrp  
25 IleThrArgGlnAsnPheSerArgCysLeuGluLeuGlnCysGlnProAspSerSerThr  
LeuGlyGlyGlySerGlyGlyGlyThrGlnAspCysSerPheGlnHisSerProIleSer  
SerAspPheAlaValLysIleArgGluLeuSerAspTyrLeuLeuGlnAspTyrProVal  
ThrValAlaSerAsnLeuGln SEQ ID NO:26;

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pMON32367.pep

35 AlaAspGluGluLeuCysGlyGlyLeuTrpArgLeuValLeuAlaGlnArgTrpMetGlu  
ArgLeuLysThrValAlaGlySerLysMetGlnGlyLeuLeuGluArgValAsnThrGlu  
IleHisPheValThrLysCysAlaPheGlnProProProSerCysLeuArgPheValGln  
ThrAsnIleSerArgLeuLeuGlnGluThrSerGluGlnLeuValAlaLeuLysProTrp  
IleThrArgGlnAsnPheSerArgCysLeuGluLeuGlnCysGlnProAspSerSerThr  
LeuGlyGlyGlySerGlyGlyGlySerGlyGlyThrGlnAspCysSerPheGlnHisSer  
ProIleSerSerAspPheAlaValLysIleArgGluLeuSerAspTyrLeuLeuGlnAsp  
40 TyrProValThrValAlaSerAsnLeuGln SEQ ID NO:27;

pMON32368.pep

45 AlaAspGluGluLeuCysGlyGlyLeuTrpArgLeuValLeuAlaGlnArgTrpMetGlu  
ArgLeuLysThrValAlaGlySerLysMetGlnGlyLeuLeuGluArgValAsnThrGlu  
IleHisPheValThrLysCysAlaPheGlnProProProSerCysLeuArgPheValGln  
ThrAsnIleSerArgLeuLeuGlnGluThrSerGluGlnLeuValAlaLeuLysProTrp  
IleThrArgGlnAsnPheSerArgCysLeuGluLeuGlnCysGlnProAspSerSerThr  
50 LeuGlyGlyGlySerGlyGlyGlySerGlyGlyGlySerGlyThrGlnAspCysSerPhe  
GlnHisSerProIleSerSerAspPheAlaValLysIleArgGluLeuSerAspTyrLeu  
LeuGlnAspTyrProValThrValAlaSerAsnLeuGln SEQ ID NO:28;

55 pMON32369.pep

AlaAspGluGluLeuCysGlyGlyLeuTrpArgLeuValLeuAlaGlnArgTrpMetGlu  
 ArgLeuLysThrValAlaGlySerLysMetGlnGlyLeuLeuGluArgValAsnThrGlu  
 IleHisPheValThrLysCysAlaPheGlnProProProSerCysLeuArgPheValGln  
 ThrAsnIleSerArgLeuLeuGlnGluThrSerGluGlnLeuValAlaLeuLysProTrp  
 5 IleThrArgGlnAsnPheSerArgCysLeuGluLeuGlnCysGlnProAspSerSerThr  
 LeuGlyGlyGlySerGlyGlyGlySerGlyGlyGlySerGlyGlyGlyThrGlnAspCys  
 SerPheGlnHisSerProIleSerSerAspPheAlaValLysIleArgGluLeuSerAsp  
 TyrLeuLeuGlnAspTyrProValThrValAlaSerAsnLeuGln SEQ ID NO:29;

10 pMON32370.pep

AlaAspGluGluLeuCysGlyGlyLeuTrpArgLeuValLeuAlaGlnArgTrpMetGlu  
 ArgLeuLysThrValAlaGlySerLysMetGlnGlyLeuLeuGluArgValAsnThrGlu  
 15 IleHisPheValThrLysCysAlaPheGlnProProProSerCysLeuArgPheValGln  
 ThrAsnIleSerArgLeuLeuGlnGluThrSerGluGlnLeuValAlaLeuLysProTrp  
 IleThrArgGlnAsnPheSerArgCysLeuGluLeuGlnCysGlnProAspSerSerThr  
 LeuGlyGlyGlySerGlyGlyGlySerGlyGlyGlySerGlyGlyGlySerGlyGlyGly  
 SerGlyThrGlnAspCysSerPheGlnHisSerProIleSerSerAspPheAlaValLys  
 20 IleArgGluLeuSerAspTyrLeuLeuGlnAspTyrProValThrValAlaSerAsnLeu  
 Gln SEQ ID NO:30;

pMON35712.pep

AlaAspTyrProValThrValAlaSerAsnLeuGlnAspGluGluLeuCysGlyGlyLeu  
 TrpArgLeuValLeuAlaGlnArgTrpMetGluArgLeuLysThrValAlaGlySerLys  
 MetGlnGlyLeuLeuGluArgValAsnThrGluIleHisPheValThrLysCysAlaPhe  
 GlnProProProSerCysLeuArgPheValGlnThrAsnIleSerArgLeuLeuGlnGlu  
 ThrSerGluGlnLeuValAlaLeuLysProTrpIleThrArgGlnAsnPheSerArgCys  
 25 LeuGluLeuGlnCysGlnProAspSerSerThrLeuGlyGlyGlySerGlyGlyGlySer  
 GlyGlyGlySerGlyGlyGlyThrGlnAspCysSerPheGlnHisSerProIleSerSer  
 AspPheAlaValLysIleArgGluLeuSerAspTyrLeuLeuGln SEQ ID NO:31;

pMON35713.pep

AlaAlaSerAsnLeuGlnAspGluGluLeuCysGlyGlyLeuTrpArgLeuValLeuAla  
 GlnArgTrpMetGluArgLeuLysThrValAlaGlySerLysMetGlnGlyLeuLeuGlu  
 ArgValAsnThrGluIleHisPheValThrLysCysAlaPheGlnProProProSerCys  
 LeuArgPheValGlnThrAsnIleSerArgLeuLeuGlnGluThrSerGluGlnLeuVal  
 35 AlaLeuLysProTrpIleThrArgGlnAsnPheSerArgCysLeuGluLeuGlnCysGln  
 ProAspSerSerThrLeuGlyGlyGlySerGlyGlyGlySerGlyGlyGlySerGlyGly  
 GlyThrGlnAspCysSerPheGlnHisSerProIleSerSerAspPheAlaValLysIle  
 ArgGluLeuSerAspTyrLeuLeuGlnAspTyrProValThrVal SEQ ID NO:32;

40 pMON35714.pep

AlaValAlaGlySerLysMetGlnGlyLeuLeuGluArgValAsnThrGluIleHisPhe  
 ValThrLysCysAlaPheGlnProProProSerCysLeuArgPheValGlnThrAsnIle  
 SerArgLeuLeuGlnGluThrSerGluGlnLeuValAlaLeuLysProTrpIleThrArg  
 45 GlnAsnPheSerArgCysLeuGluLeuGlnCysGlnProAspSerSerThrLeuGlyGly  
 GlySerGlyGlyGlySerGlyGlyGlySerGlyGlyGlyThrGlnAspCysSerPheGln  
 HisSerProIleSerSerAspPheAlaValLysIleArgGluLeuSerAspTyrLeuLeu  
 GlnAspTyrProValThrValAlaSerAsnLeuGlnAspGluGluLeuCysGlyGlyLeu  
 TrpArgLeuValLeuAlaGlnArgTrpMetGluArgLeuLysThr SEQ ID NO:33;

50 pMON35715.pep

AlaSerLysMetGlnGlyLeuLeuGluArgValAsnThrGluIleHisPheValThrLys  
 CysAlaPheGlnProProProSerCysLeuArgPheValGlnThrAsnIleSerArgLeu  
 LeuGlnGluThrSerGluGlnLeuValAlaLeuLysProTrpIleThrArgGlnAsnPhe  
 5 SerArgCysLeuGluLeuGlnCysGlnProAspSerSerThrLeuGlyGlyGlySerGly  
 GlyGlySerGlyGlyGlySerGlyGlyGlyThrGlnAspCysSerPheGlnHisSerPro  
 IleSerSerAspPheAlaValLysIleArgGluLeuSerAspTyrLeuLeuGlnAspTyr  
 ProValThrValAlaSerAsnLeuGlnAspGluGluLeuCysGlyGlyLeuTrpArgLeu  
 ValLeuAlaGlnArgTrpMetGluArgLeuLysThrValAlaGly SEQ ID NO:34;

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pMON35716.pep

AlaProProSerCysLeuArgPheValGlnThrAsnIleSerArgLeuLeuGlnGluThr  
 SerGluGlnLeuValAlaLeuLysProTrpIleThrArgGlnAsnPheSerArgCysLeu  
 15 GluLeuGlnCysGlnProAspSerSerThrLeuGlyGlyGlySerGlyGlyGlySerGly  
 GlyGlySerGlyGlyGlyThrGlnAspCysSerPheGlnHisSerProIleSerSerAsp  
 PheAlaValLysIleArgGluLeuSerAspTyrLeuLeuGlnAspTyrProValThrVal  
 AlaSerAsnLeuGlnAspGluGluLeuCysGlyGlyLeuTrpArgLeuValLeuAlaGln  
 ArgTrpMetGluArgLeuLysThrValAlaGlySerLysMetGlnGlyLeuLeuGluArg  
 20 ValAsnThrGluIleHisPheValThrLysCysAlaPheGlnPro SEQ ID NO:35;

pMON35717.pep

AlaArgPheValGlnThrAsnIleSerArgLeuLeuGlnGluThrSerGluGlnLeuVal  
 25 AlaLeuLysProTrpIleThrArgGlnAsnPheSerArgCysLeuGluLeuGlnCysGln  
 ProAspSerSerThrLeuGlyGlyGlySerGlyGlyGlySerGlyGlyGlySerGlyGly  
 GlyThrGlnAspCysSerPheGlnHisSerProIleSerSerAspPheAlaValLysIle  
 ArgGluLeuSerAspTyrLeuLeuGlnAspTyrProValThrValAlaSerAsnLeuGln  
 AspGluGluLeuCysGlyGlyLeuTrpArgLeuValLeuAlaGlnArgTrpMetGluArg  
 30 LeuLysThrValAlaGlySerLysMetGlnGlyLeuLeuGluArgValAsnThrGluIle  
 HisPheValThrLysCysAlaPheGlnProProProSerCysLeu SEQ ID NO:36;

pMON35718.pep

AlaThrAsnIleSerArgLeuLeuGlnGluThrSerGluGlnLeuValAlaLeuLysPro  
 35 TrpIleThrArgGlnAsnPheSerArgCysLeuGluLeuGlnCysGlnProAspSerSer  
 ThrLeuGlyGlyGlySerGlyGlyGlySerGlyGlyGlySerGlyGlyGlyThrGlnAsp  
 CysSerPheGlnHisSerProIleSerSerAspPheAlaValLysIleArgGluLeuSer  
 AspTyrLeuLeuGlnAspTyrProValThrValAlaSerAsnLeuGlnAspGluGluLeu  
 40 CysGlyGlyLeuTrpArgLeuValLeuAlaGlnArgTrpMetGluArgLeuLysThrVal  
 AlaGlySerLysMetGlnGlyLeuLeuGluArgValAsnThrGluIleHisPheValThr  
 LysCysAlaPheGlnProProProSerCysLeuArgPheValGln SEQ ID NO:37;

45

## Materials and Methods

### Recombinant DNA methods

Unless noted otherwise, all specialty chemicals  
5 were obtained from Sigma Co., (St. Louis, MO).  
Restriction endonucleases and T4 DNA ligase were  
obtained from New England Biolabs (Beverly, MA) or  
Boehringer Mannheim (Indianapolis, IN).

### 10 Transformation of *E. coli* strains

*E. coli* strains, such as DH5 $\alpha$ <sup>TM</sup> (Life Technologies,  
Gaithersburg, MD) and TG1 (Amersham Corp., Arlington  
Heights, IL) are used for transformation of ligation  
15 reactions and are the source of plasmid DNA for  
transfecting mammalian cells. *E. coli* strains, such as  
MON105 and JM101, can be used for expressing the flt3  
receptor agonist of the present invention in the  
cytoplasm or periplasmic space.

20

MON105 ATCC#55204: F<sup>-</sup>, lamda<sup>-</sup>, IN(rrnD, rrE)1, rpoD<sup>+</sup>,  
rpoH358

DH5 $\alpha$ <sup>TM</sup>: F<sup>-</sup>, phi80dlacZdeltaM15, delta(lacZYA-argF)U169,  
25 deoR, recA1, endA1, hsdR17(rk<sup>-</sup>,mk<sup>+</sup>), phoA, supE44lamda<sup>-</sup>,  
thi-1, gyrA96, relA1

TG1: delta(lac-pro), supE, thi-1, hsdD5/F'(traD36,  
proA+B<sup>+</sup>, lacIq, lacZdeltaM15)

30

DH5 $\alpha$ <sup>TM</sup> Subcloning efficiency cells are purchased as  
competent cells and are ready for transformation using  
the manufacturer's protocol, while both *E. coli* strains  
TG1 and MON105 are rendered competent to take up DNA  
35 using a CaCl<sub>2</sub> method. Typically, 20 to 50 mL of cells  
are grown in LB medium (1% Bacto-tryptone, 0.5% Bacto-  
yeast extract, 150 mM NaCl) to a density of

approximately 1.0 optical density unit at 600 nanometers (OD600) as measured by a Baush & Lomb Spectronic spectrophotometer (Rochester, NY). The cells are collected by centrifugation and resuspended in one-fifth culture volume of  $\text{CaCl}_2$  solution (50 mM  $\text{CaCl}_2$ , 10 mM Tris-Cl, pH 7.4) and are held at 4°C for 30 minutes. The cells are again collected by centrifugation and resuspended in one-tenth culture volume of  $\text{CaCl}_2$  solution. Ligated DNA is added to 0.2mL of these cells, and the samples are held at 4°C for 1 hour. The samples are shifted to 42°C for two minutes and 1mL of LB is added prior to shaking the samples at 37°C for one hour. Cells from these samples are spread on plates (LB medium plus 1.5% Bacto-agar) containing either ampicillin (100 micrograms/mL, ug/mL) when selecting for ampicillin-resistant transformants, or spectinomycin (75 ug/mL) when selecting for spectinomycin-resistant transformants. The plates are incubated overnight at 37°C. Single colonies are picked, grown in LB supplemented with appropriate antibiotic for 6-16 hours at 37°C with shaking. Colonies are picked and inoculated into LB plus appropriate antibiotic (100 ug/mL ampicillin or 75 ug/mL spectinomycin) and are grown at 37°C while shaking. Before harvesting the cultures, 1 ul of cells are analyzed by PCR for the presence of a *flt3* receptor agonist gene. The PCR is carried out using a combination of primers that anneal to the *flt3* receptor agonist gene and/or vector. After the PCR is complete, loading dye is added to the sample followed by electrophoresis as described earlier. A gene has been ligated to the vector when a PCR product of the expected size is observed.

Methods for creation of genes with new N-terminus/C-terminus

Method I. Creation of genes with new N-terminus/C-terminus which contain a linker region.

Genes with new N-terminus/C-terminus which contain  
5 a linker region separating the original C-terminus and  
N-terminus can be made essentially following the method  
described in L. S. Mullins, et al *J. Am. Chem. Soc.* **116**,  
5529-5533 (1994). Multiple steps of polymerase chain  
10 DNA sequence encoding the primary amino acid sequence of  
the protein. The steps are illustrated in Figure 2.

In the first step, the primer set ("new start" and  
"linker start") is used to create and amplify, from the  
15 original gene sequence, the DNA fragment ("Fragment  
Start") that contains the sequence encoding the new N-  
terminal portion of the new protein followed by the  
linker that connects the C-terminal and N-terminal ends  
of the original protein. In the second step, the primer  
20 set ("new stop" and "linker stop") is used to create and  
amplify, from the original gene sequence, the DNA  
fragment ("Fragment Stop") that encodes the same linker  
as used above, followed by the new C-terminal portion of  
the new protein. The "new start" and "new stop" primers  
25 are designed to include the appropriate restriction  
enzyme recognition sites which allow cloning of the new  
gene into expression plasmids. Typical PCR conditions  
are one cycle 95°C melting for two minutes; 25 cycles  
94°C denaturation for one minute, 50°C annealing for one  
30 minute and 72°C extension for one minute; plus one cycle  
72°C extension for seven minutes. A Perkin Elmer  
GeneAmp PCR Core Reagents kit is used. A 100 ul  
reaction contains 100 pmole of each primer and one ug of  
template DNA; and 1x PCR buffer, 200 uM dGTP, 200 uM  
35 dATP, 200 uM dTTP, 200 uM dCTP, 2.5 units AmpliTaq DNA  
polymerase and 2 mM MgCl<sub>2</sub>. PCR reactions are performed

in a Model 480 DNA thermal cycler (Perkin Elmer Corporation, Norwalk, CT).

"Fragment Start" and "Fragment Stop", which have  
5 complementary sequence in the linker region and the  
coding sequence for the two amino acids on both sides of  
the linker, are joined together in a third PCR step to  
make the full-length gene encoding the new protein. The  
DNA fragments "Fragment Start" and "Fragment Stop" are  
10 resolved on a 1% TAE gel, stained with ethidium bromide  
and isolated using a Qiaex Gel Extraction kit (Qiagen).  
These fragments are combined in equimolar quantities,  
heated at 70°C for ten minutes and slow cooled to allow  
annealing through their shared sequence in "linker  
15 start" and "linker stop". In the third PCR step,  
primers "new start" and "new stop" are added to the  
annealed fragments to create and amplify the full-length  
new N-terminus/C-terminus gene. Typical PCR conditions  
are one cycle 95°C melting for two minutes; 25 cycles  
20 94°C denaturation for one minute, 60°C annealing for one  
minute and 72°C extension for one minute; plus one cycle  
72°C extension for seven minutes. A Perkin Elmer  
GeneAmp PCR Core Reagents kit is used. A 100 ul  
reaction contains 100 pmole of each primer and  
25 approximately 0.5 ug of DNA; and 1x PCR buffer, 200 uM  
dGTP, 200 uM dATP, 200 uM dTTP, 200 uM dCTP, 2.5 units  
AmpliTaq DNA polymerase and 2 mM MgCl<sub>2</sub>. PCR reactions  
are purified using a Wizard PCR Preps kit (Promega).  
30 Method II. Creation of genes with new N-terminus/C-  
terminus without a linker region.

New N-terminus/C-terminus genes without a linker  
joining the original N-terminus and C-terminus can be  
35 made using two steps of PCR amplification and a blunt  
end ligation. The steps are illustrated in Figure 3.  
In the first step, the primer set ("new start" and "P-bl

start") is used to create and amplify, from the original gene sequence, the DNA fragment ("Fragment Start") that contains the sequence encoding the new N-terminal portion of the new protein. In the second step, the primer set ("new stop" and "P-bl stop") is used to create and amplify, from the original gene sequence, the DNA fragment ("Fragment Stop") that contains the sequence encoding the new C-terminal portion of the new protein. The "new start" and "new stop" primers are designed to include appropriate restriction sites which allow cloning of the new gene into expression vectors. Typical PCR conditions are one cycle 95°C melting for two minutes; 25 cycles 94°C denaturation for one minute, 50°C annealing for 45 seconds and 72°C extension for 45 seconds. Deep Vent polymerase (New England Biolabs) is used to reduce the occurrence of overhangs in conditions recommended by the manufacturer. The "P-bl start" and "P-bl stop" primers are phosphorylated at the end to aid in the subsequent blunt end ligation of "Fragment Start" and "Fragment Stop" to each other. A 100 ul reaction contained 150 pmole of each primer and one ug of template DNA; and 1x Vent buffer (New England Biolabs), 300 uM dGTP, 300 uM dATP, 300 uM dTTP, 300 uM dCTP, and 1 unit Deep Vent polymerase. PCR reactions are performed in a Model 480 DNA thermal cycler (Perkin Elmer Corporation, Norwalk, CT). PCR reaction products are purified using a Wizard PCR Preps kit (Promega).

The primers are designed to include appropriate restriction enzyme recognition sites which allow for the cloning of the new gene into expression vectors. Typically "Fragment Start" is designed to create a NcoI restriction site, and "Fragment Stop" is designed to create a HindIII restriction site. Restriction digest reactions are purified using a Magic DNA Clean-up System kit (Promega). Fragments Start and Stop are resolved on a 1% TAE gel, stained with ethidium bromide and isolated

using a Qiaex Gel Extraction kit (Qiagen). These fragments are combined with and annealed to the ends of the ~ 3800 base pair NcoI/HindIII vector fragment of pMON3934 by heating at 50°C for ten minutes and allowed  
5 to slow cool. The three fragments are ligated together using T4 DNA ligase (Boehringer Mannheim). The result is a plasmid containing the full-length new N-terminus/C-terminus gene. A portion of the ligation reaction is used to transform *E. coli* strain DH5 $\alpha$  cells (Life  
10 Technologies, Gaithersburg, MD). Plasmid DNA is purified and sequence confirmed as below.

Method III. Creation of new N-terminus/C-terminus genes by tandem-duplication method

15

New N-terminus/C-terminus genes can be made based on the method described in R. A. Horlick, et al *Protein Eng.* 5:427-431 (1992). Polymerase chain reaction (PCR) amplification of the new N-terminus/C-terminus genes is  
20 performed using a tandemly duplicated template DNA. The steps are illustrated in Figure 4.

The tandemly-duplicated template DNA is created by cloning and contains two copies of the gene separated by  
25 DNA sequence encoding a linker connecting the original C- and N-terminal ends of the two copies of the gene. Specific primer sets are used to create and amplify a full-length new N terminus/C-terminus gene from the tandemly-duplicated template DNA. These primers are  
30 designed to include appropriate restriction sites which allow for the cloning of the new gene into expression vectors. Typical PCR conditions are one cycle 95°C melting for two minutes; 25 cycles 94°C denaturation for one minute, 50°C annealing for one minute and 72°C  
35 extension for one minute; plus one cycle 72°C extension for seven minutes. A Perkin Elmer GeneAmp PCR Core Reagents kit (Perkin Elmer Corporation, Norwalk, CT) is

used. A 100 ul reaction contains 100 pmole of each primer and one ug of template DNA; and 1x PCR buffer, 200 uM dGTP, 200 uM dATP, 200 uM dTTP, 200 uM dCTP, 2.5 units AmpliTaq DNA polymerase and 2 mM MgCl<sub>2</sub>. PCR reactions are performed in a Model 480 DNA thermal cyclor (Perkin Elmer Corporation, Norwalk, CT). PCR reactions are purified using a Wizard PCR Preps kit (Promega).

#### 10 DNA isolation and characterization

Plasmid DNA can be isolated by a number of different methods and using commercially available kits known to those skilled in the art. A few such methods are shown herein. Plasmid DNA is isolated using the Promega Wizard™ Miniprep kit (Madison, WI), the Qiagen QIAwell Plasmid isolation kits (Chatsworth, CA) or Qiagen Plasmid Midi kit. These kits follow the same general procedure for plasmid DNA isolation. Briefly, cells are pelleted by centrifugation (5000 x g), plasmid DNA released with sequential NaOH/acid treatment, and cellular debris is removed by centrifugation (10000 x g). The supernatant (containing the plasmid DNA) is loaded onto a column containing a DNA-binding resin, the column is washed, and plasmid DNA eluted with TE. After screening for the colonies with the plasmid of interest, the *E. coli* cells are inoculated into 50-100 mLs of LB plus appropriate antibiotic for overnight growth at 37°C in an air incubator while shaking. The purified plasmid DNA is used for DNA sequencing, further restriction enzyme digestion, additional subcloning of DNA fragments and transfection into mammalian, *E. coli* or other cells.

#### 35 Sequence confirmation.

Purified plasmid DNA is resuspended in dH<sub>2</sub>O and quantitated by measuring the absorbance at 260/280 nm in a Bausch and Lomb Spectronic 601 UV spectrometer. DNA

samples are sequenced using ABI PRISM™ DyeDeoxy™ terminator sequencing chemistry (Applied Biosystems Division of Perkin Elmer Corporation, Lincoln City, CA) kits (Part Number 401388 or 402078) according to the  
5 manufacturers suggested protocol usually modified by the addition of 5% DMSO to the sequencing mixture. Sequencing reactions are performed in a Model 480 DNA thermal cycler (Perkin Elmer Corporation, Norwalk, CT) following the recommended amplification conditions.  
10 Samples are purified to remove excess dye terminators with Centri-Sep™ spin columns (Princeton Separations, Adelphia, NJ) and lyophilized. Fluorescent dye labeled sequencing reactions are resuspended in deionized formamide, and sequenced on denaturing 4.75%  
15 polyacrylamide-8M urea gels using an ABI Model 373A automated DNA sequencer. Overlapping DNA sequence fragments are analyzed and assembled into master DNA contigs using Sequencher DNA analysis software (Gene Codes Corporation, Ann Arbor, MI).

20

Expression of flt3 receptor agonists in mammalian cells

Mammalian Cell Transfection/Production of Conditioned Media

25

The BHK-21 cell line can be obtained from the ATCC (Rockville, MD). The cells are cultured in Dulbecco's modified Eagle media (DMEM/high-glucose), supplemented to 2mM (mM) L-glutamine and 10% fetal bovine serum  
30 (FBS). This formulation is designated BHK growth media. Selective media is BHK growth media supplemented with 453 units/mL hygromycin B (Calbiochem, San Diego, CA). The BHK-21 cell line was previously stably transfected with the HSV transactivating protein VP16, which  
35 transactivates the IE110 promoter found on the plasmid pMON3359 (See Hippenmeyer et al., *Bio/Technology*, pp.1037-1041, 1993). The VP16 protein drives expression

of genes inserted behind the IE110 promoter. BHK-21 cells expressing the transactivating protein VP16 are designated BHK-VP16. The plasmid pMON1118 (See Highkin et al., *Poultry Sci.*, **70**: 970-981, 1991) expresses the  
5 hygromycin resistance gene from the SV40 promoter. A similar plasmid is available from ATCC, pSV2-hph.

BHK-VP16 cells are seeded into a 60 millimeter (mm) tissue culture dish at  $3 \times 10^5$  cells per dish 24 hours prior to transfection. Cells are transfected for 16  
10 hours in 3 mL of "OPTIMEM"™ (Gibco-BRL, Gaithersburg, MD) containing 10 ug of plasmid DNA containing the gene of interest, 3 ug hygromycin resistance plasmid, pMON1118, and 80 ug of Gibco-BRL "LIPOFECTAMINE"™ per dish. The media is subsequently aspirated and replaced  
15 with 3 mL of growth media. At 48 hours post-transfection, media from each dish is collected and assayed for activity (transient conditioned media). The cells are removed from the dish by trypsin-EDTA, diluted 1:10 and transferred to 100 mm tissue culture dishes  
20 containing 10 mL of selective media. After approximately 7 days in selective media, resistant cells grow into colonies several millimeters in diameter. The colonies are removed from the dish with filter paper (cut to approximately the same size as the colonies and soaked  
25 in trypsin/EDTA) and transferred to individual wells of a 24 well plate containing 1 mL of selective media. After the clones are grown to confluence, the conditioned media is re-assayed, and positive clones are expanded into growth media.

30

#### Expression of flt3 receptor agonists in *E. coli*

*E. coli* strain MON105 or JM101 harboring the plasmid of interest are grown at 37°C in M9 plus  
35 casamino acids medium with shaking in a air incubator Model G25 from New Brunswick Scientific (Edison, New Jersey). Growth is monitored at OD600 until it reaches

a value of 1, at which time nalidixic acid (10 milligrams/mL) in 0.1 N NaOH is added to a final concentration of 50 µg/mL. The cultures are then shaken at 37°C for three to four additional hours. A high degree of aeration is maintained throughout culture period in order to achieve maximal production of the desired gene product. The cells are examined under a light microscope for the presence of inclusion bodies (IB). One mL aliquots of the culture are removed for analysis of protein content by boiling the pelleted cells, treating them with reducing buffer and electrophoresis via SDS-PAGE (see Maniatis et al. Molecular Cloning: A Laboratory Manual, 1982). The culture is centrifuged (5000 x g) to pellet the cells. Additional strategies for achieving high-level expression of genes in *E. coli* can be found in Savvas, C.M. (*Microbiological Reviews* **60**;512-538, 1996).

Inclusion Body preparation, Extraction, Refolding, Dialysis, DEAE Chromatography, and Characterization of the flt3 receptor agonists which accumulate as inclusion bodies in *E. coli*.

#### Isolation of Inclusion Bodies:

The cell pellet from a 330 mL *E. coli* culture is resuspended in 15 mL of sonication buffer (10 mM 2-amino-2-(hydroxymethyl) 1,3-propanediol hydrochloride (Tris-HCl), pH 8.0 + 1 mM ethylenediaminetetraacetic acid (EDTA)). These resuspended cells are sonicated using the microtip probe of a Sonicator Cell Disruptor (Model W-375, Heat Systems-Ultrasonics, Inc., Farmingdale, New York). Three rounds of sonication in sonication buffer followed by centrifugation are employed to disrupt the cells and wash the inclusion bodies (IB). The first round of sonication is a 3

minute burst followed by a 1 minute burst, and the final two rounds of sonication are for 1 minute each.

Extraction and refolding of proteins from inclusion body  
5 pellets:

Following the final centrifugation step, the IB pellet is resuspended in 10 mL of 50 mM Tris-HCl, pH 9.5, 8 M urea and 5 mM dithiothreitol (DTT) and stirred  
10 at room temperature for approximately 45 minutes to allow for denaturation of the expressed protein.

The extraction solution is transferred to a beaker containing 70 mL of 5mM Tris-HCl, pH 9.5 and 2.3 M urea and gently stirred while exposed to air at 4°C for 18 to  
15 48 hours to allow the proteins to refold. Refolding is monitored by analysis on a Vydac (Hesperia, Ca.) C18 reversed phase high pressure liquid chromatography (RP-HPLC) column (0.46x25 cm). A linear gradient of 40% to 65% acetonitrile, containing 0.1% trifluoroacetic acid  
20 (TFA), is employed to monitor the refold. This gradient is developed over 30 minutes at a flow rate of 1.5 mL per minute. Denatured proteins generally elute later in the gradient than the refolded proteins.

25 Purification:

Following the refold, contaminating *E. coli* proteins are removed by acid precipitation. The pH of the refold solution is titrated to between pH 5.0 and pH  
30 5.2 using 15% (v/v) acetic acid (HOAc). This solution is stirred at 4°C for 2 hours and then centrifuged for 20 minutes at 12,000 x g to pellet any insoluble protein.

The supernatant from the acid precipitation step is  
35 dialyzed using a Spectra/Por 3 membrane with a molecular weight cut off (MWCO) of 3,500 daltons. The dialysis is against 2 changes of 4 liters (a 50-fold excess) of 10mM

Tris-HCl, pH 8.0 for a total of 18 hours. Dialysis lowers the sample conductivity and removes urea prior to DEAE chromatography. The sample is then centrifuged (20 minutes at 12,000 x g) to pellet any insoluble protein following dialysis.

A Bio-Rad Bio-Scale DEAE2 column (7 x 52 mm) is used for ion exchange chromatography. The column is equilibrated in a buffer containing 10mM Tris-HCl, pH 8.0. The protein is eluted using a 0-to-500 mM sodium chloride (NaCl) gradient, in equilibration buffer, over 45 column volumes. A flow rate of 1 mL per minute is used throughout the run. Column fractions (2 mL per fraction) are collected across the gradient and analyzed by RP HPLC on a Vydac (Hesperia, Ca.) C18 column (0.46 x 25 cm). A linear gradient of 40% to 65% acetonitrile, containing 0.1% trifluoroacetic acid (TFA), is employed. This gradient is developed over 30 minutes at a flow rate of 1.5 mL per minute. Pooled fractions are then dialyzed against 2 changes of 4 liters (50-to-500-fold excess) of 10 mM ammonium acetate (NH<sub>4</sub>Ac), pH 4.0 for a total of 18 hours. Dialysis is performed using a Spectra/Por 3 membrane with a MWCO of 3,500 daltons. Finally, the sample is sterile filtered using a 0.22µm syringe filter (µStar LB syringe filter, Costar, Cambridge, Ma.), and stored at 4°C.

In some cases the folded proteins can be affinity purified using affinity reagents such as mAbs or receptor subunits attached to a suitable matrix. Alternatively, (or in addition) purification can be accomplished using any of a variety of chromatographic methods such as: ion exchange, gel filtration or hydrophobic chromatography or reversed phase HPLC.

These and other protein purification methods are described in detail in Methods in Enzymology, Volume 182 'Guide to Protein Purification' edited by Murray Deutscher, Academic Press, San Diego, CA (1990).

#### Protein Characterization:

The purified protein is analyzed by RP-HPLC,  
5 electrospray mass spectrometry, and SDS-PAGE. The  
protein quantitation is done by amino acid composition,  
RP-HPLC, and Bradford protein determination. In some  
cases tryptic peptide mapping is performed in  
conjunction with electrospray mass spectrometry to  
10 confirm the identity of the protein.

#### Methylcellulose Assay

This assay reflects the ability of colony stimulating  
15 factors to stimulate normal bone marrow cells to produce  
different types of hematopoietic colonies *in vitro*  
(Bradley et al., *Aust. Exp Biol. Sci.* **44**:287-300,  
1966), Pluznik et al., *J. Cell Comp. Physio* **66**:319-324,  
1965).

20

#### Methods

Approximately 30 mL of fresh, normal, healthy bone  
marrow aspirate are obtained from individuals following  
informed consent. Under sterile conditions samples are  
25 diluted 1:5 with a 1X PBS (#14040.059 Life Technologies,  
Gaithersburg, MD.) solution in a 50 mL conical tube  
(#25339-50 Corning, Corning MD). Ficoll (Histopaque  
1077 Sigma H-8889) is layered under the diluted sample  
and centrifuged, 300 x g for 30 min. The mononuclear  
30 cell band is removed and washed two times in 1X PBS and  
once with 1% BSA PBS (CellPro Co., Bothel, WA).  
Mononuclear cells are counted and CD34+ cells are  
selected using the Ceparate LC (CD34) Kit (CellPro Co.,  
Bothel, WA) column. This fractionation is performed  
35 since all stem and progenitor cells within the bone  
marrow display CD34 surface antigen..

Cultures are set up in triplicate with a final volume of 1.0 mL in a 35 X 10 mm petri dish (Nunc#174926). Culture medium is purchased from Terry Fox Labs. (HCC-4230 medium (Terry Fox Labs, Vancouver, B.C., Canada) and erythropoietin (Amgen, Thousand Oaks, CA.) is added to the culture media. 3,000-10,000 CD34+ cells are added per dish. FLT3 receptor agonist proteins, in conditioned media from transfected mammalian cells or purified from conditioned media from transfected mammalian cells or *E. coli*, are added to give final concentrations ranging from .001 nM to 10 nM. Cultures are resuspended using a 3cc syringe and 1.0 mL is dispensed per dish. Control (baseline response) cultures received no colony stimulating factors. Positive control cultures received conditioned media (PHA stimulated human cells: Terry Fox Lab. H2400). Cultures are incubated at 37°C, 5% CO<sub>2</sub> in humidified air.

Hematopoietic colonies which are defined as greater than 50 cells are counted on the day of peak response (days 10-11) using a Nikon inverted phase microscope with a 40x objective combination. Groups of cells containing fewer than 50 cells are referred to as clusters. Alternatively colonies can be identified by spreading the colonies on a slide and stained or they can be picked, resuspended and spun onto cytospin slides for staining.

#### Human Cord Blood Hemopoietic Growth Factor Assays

Bone marrow cells are traditionally used for in vitro assays of hematopoietic colony stimulating factor (CSF) activity. However, human bone marrow is not always available, and there is considerable variability between donors. Umbilical cord blood is comparable to bone marrow as a source of hematopoietic stem cells and progenitors (Broxmeyer et al., *PNAS USA* **89**:4109-113,

1992; Mayani et al., *Blood* **81**:3252-3258, 1993). In contrast to bone marrow, cord blood is more readily available on a regular basis. There is also a potential to reduce assay variability by pooling cells obtained  
5 fresh from several donors, or to create a bank of cryopreserved cells for this purpose.

#### Methods

Mononuclear cells (MNC) are isolated from cord blood  
10 within 24 hr. of collection, using a standard density gradient (1.077 g/mL Histopaque). Cord blood MNC have been further enriched for stem cells and progenitors by several procedures, including immunomagnetic selection for CD14-, CD34+ cells; panning for SBA-, CD34+  
15 fraction using coated flasks from Applied Immune Science (Santa Clara, CA); and CD34+ selection using a CellPro (Bothell, WA) avidin column. Either freshly isolated or cryopreserved CD34+ cell enriched fractions are used for the assay. Duplicate cultures for each serial dilution  
20 of sample (concentration range from 1 pM to 1204 pM) are prepared with 1x10<sup>4</sup> cells in 1ml of 0.9% methylcellulose containing medium without additional growth factors (Methocult H4230 from Stem Cell Technologies, Vancouver, BC.). In some experiments, Methocult H4330 containing  
25 erythropoietin (FLT3) was used instead of Methocult H4230, or Stem Cell Factor (SCF), 50 ng/mL (Biosource International, Camarillo, CA) was added. After culturing for 7-9 days, colonies containing >30 cells are counted.

#### 30 MUTZ-2 Cell Proliferation Assay

A cell line such as MUTZ-2, which is a human myeloid leukemia cell line (German Collection of Microorganisms and Cell Cultures, DSM ACC 271), can be used to  
35 determine the cell proliferative activity of flt3 receptor agonists. MUTZ-2 cultures are maintained with recombinant native flt3 ligand (20-100ng/mL) in the

growth medium. Eighteen hours prior to assay set-up, MUTZ-2 cells are washed in IMDM medium (Gibco) three times and are resuspended in IMDM medium alone at a concentration of  $0.5-0.7 \times 10^6$  cells/mL and incubated at  $37^\circ\text{C}$  and  $5\%\text{CO}_2$  to starve the cells of flt3 ligand. The day of the assay, standards and flt3 receptor agonists are diluted to two fold above desired final concentration in assay media in sterile tissue culture treated 96 well plates. Flt3 receptor agonists and standards are tested in triplicate. 50 $\mu\text{l}$  of assay media is loaded into all wells except row A. 75 $\mu\text{l}$  of the flt3 receptor agonists or standards are added to row A and 25 $\mu\text{l}$  taken from that row and serial dilutions (1:3) performed on the rest of the plate (rows B through G). Row H remains as a media only control. The starved MUTZ-2 cells are washed two times in IMDM medium and resuspended in 50 $\mu\text{l}$  assay media. 50 $\mu\text{l}$  of cells are added to each well resulting in a final concentration of  $0.25 \times 10^6$  cells/mL. Assay plates containing cells are incubated at  $37^\circ\text{C}$  and  $5\%\text{CO}_2$  for 44hrs. Each well is then pulsed with 1 $\mu\text{Ci}$ /well of tritiated thymidine in a volume of 20 $\mu\text{l}$  for four hours. Plates are then harvested and counted.

#### 25 Transfected cell lines:

Cell lines, such as BHK or the murine pro B cell line Baf/3, can be transfected with a colony stimulating factor receptor, such as the human flt3 receptor which the cell line does not have. These transfected cell lines can be used to determine the activity of the ligand of which the receptor has been transfected.

#### EXAMPLE 1

35

#### Isolation of cDNA encoding flt3 ligand

Three flt3 ligand clones were amplified from human bone marrow poly A+ RNA (Clontech) using NCOFLT, HIND160, and HIND165 PCR primers (according to the manufacturer's suggested conditions). These amplified PCR products were gel purified and cloned into the BHK expression vector pMON5723 generating pMON30237 (NCOFLT + HIND160), pMON30238 (NCOFLT + HIND165), and a deletion clone pMON30239 (NCOFLT + HIND165). The deletion in pMON30239 is of amino acid residues 89 through 106 (the numbering of the residues is based on the sequence of native flt3 ligand as shown in Figure 5a and 5b).

#### EXAMPLE 2

Sequence rearranged flt3 ligand were constructed using several methods and linker types. The first set of constructs containing the linker peptide (SerGlyGlyAsnGly)X (where X = 1, 2, or 3) with the breakpoints 39/40, 65/66, and 89/90 were made using a two step PCR process described by Mullins et al. in which the front half and the back half of each final sequence rearranged molecule is made separately in the first PCR step, then the paired products of the first reaction step are combined in a second PCR step and extended in the absence of exogenous primers. For example, to make the three 89/90 breakpoint precursor molecules with the SerGlyGlyAsnGly SEQ ID NO:46, SerGlyGlyAsnGlySerGlyGlyAsnGly SEQ ID NO:47, and SerGlyGlyAsnGlySerGlyGlyAsnGlySerGlyGlyAsnGly SEQ ID NO:48 amino acid linkers (pMON32326, pMON32327 and pMON32328 respectively), six initial PCR products were generated. The following primer pairs were used in the first step PCR reaction: a) 89For/L5B; b) 89For/L10B; c) 89For/L15B; d) 89Rev/L5A; e) 89Rev/L10A; and f) 89Rev/L15A. The identical approach was used to make pMON32321 (39/40 breakpoint, primer pairs 39For/L10B and

39Rev/L10A) and pMON32325 (65/66 breakpoint, primer pairs 65For/L5B and 65Rev/L5A) precursors. Except as noted below, all subsequent PCR reactions utilized the components of the PCR Optimizer Kit (Invitrogen) and  
5 amplification conditions according to the manufacturers suggested protocol. Reactions were set up as follows: 50 pmole of each primer, 10 ul of 5X Buffer B [300 mM Tris-HCl (pH 8.5), 10 mM MgCl<sub>2</sub>, 75 mM (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub>], 5 U Taq polymerase, and 100 ng of heat denatured DNA (in  
10 this example pMON30238) template were combined, and brought to 45 ul final volume with dH<sub>2</sub>O. Reactions were pre-incubated for 1-5 minute at 80°C, then 5 ul of 10 mM dNTP added to each reaction, and heat denatured for 2 minutes at 94°C prior to amplification in a Perkin Elmer  
15 model 480 DNA thermal cycler. Seven DNA amplification cycles were done under the following conditions: heat denature for one minute at 94°C, two minutes annealing at 65°C, followed by a three minute extension at 72°C. Twenty three additional cycles consisting of a one  
20 minute heat denaturation at 94°C followed by a four minute annealing/extension at 72°C were done, followed by a final 7 minute extension cycle at 72°C. With the exception of pMON32328, the PCR amplification products were run out on a 1.2% TAE agarose gel, and the  
25 appropriate size bands (the major amplification product) were excised and purified using Geneclean II (Bio 101). Samples were resuspended in 10 ul dH<sub>2</sub>O. The amplification products for pMON32328 were purified directly using a Wizard PCR Clean UP kit (Promega), and  
30 DNA eluted in 50 ul dH<sub>2</sub>O. The method to construct the precursors of pMON32322 (39/40 breakpoint, primer pairs 39For/L5B and 39Rev/L5A) was modified by increasing the amount of template to 1 ug, and by changing the PCR amplification conditions as  
35 follows: six cycles of 94°C, 1 minute, 65°C for 2 minute, and 72°C for 2 1/2 minutes, followed by 15 cycles of 94°C for 1 minute, 70°C for 2 minutes, and

72°C for 2 minutes, followed by a single 72°C extension cycle for seven minutes.

The second PCR step utilized the gel-purified precursors from the first PCR step as a combination of

5 primer/template as follows: 5 ul each of each precursor molecule (i.e. for pMON32328 the PCR products from primer pairs 89For/L5B and 89Rev/L5A), 10 ul of 5X Buffer B, 5 U of Taq polymerase, and 24 ul dH<sub>2</sub>O. The reactions were heated for five minutes at 80°C, 5 ul of  
10 10 mM dNTP was added, and the reactions heat denatured for 94°C for two minutes. DNA amplification conditions were as follows: 15 cycles of 94°C for one minute, 69°C for two minutes, followed then by a three minute extension at 72°C. To allow for complete extension, the  
15 last cycle was followed by a single extension step at 72°C for seven minutes. The 80 deg incubation time was reduced to two minutes and the number of cycles was decreased to ten cycles for pMON32325 (PCR products 65For/L5B and 65Rev/L5A). PCR reaction products of the  
20 appropriate size were gel purified on a 1.2 % TAE agarose gel using Geneclean II. For pMON32322 (39For/L5B and 39Rev/L5A) the annealing temperature was reduced to 68°C, and the extension time reduced to two minutes. In addition, the PCR product was purified using a Wizard  
25 PCR Clean Up kit (Promega) according to the suppliers suggested protocol. The second PCR step was modified for pMON32326 (PCR products of 89For/L15B and 89Rev/L15A) as follows. Three sets of PCR reactions were set up identically as above, except for the sample  
30 buffer type (either 5X buffer B, D, or J - PCR Optimizer Kit). Composition of buffers D and J differ from buffer B only by pH or [MgCl<sub>2</sub>]. The [MgCl<sub>2</sub>] for buffer D is 3.5 mM, whereas the pH of buffer J is 9.5. The protocol was modified by increasing the number of PCR cycles 20, and 15 ul aliquots were withdrawn at the end of cycles  
35 10, 15 and 20. Five uls of each aliquot timepoint were analyzed for the presence of amplified material on a

1.2% TBE agarose gel. The remainder of the buffer B, D, and J PCR reaction mixtures were pooled and subsequently purified using the Wizard PCR Clean Up Kit protocol. The DNA was eluted in 50 ul dH<sub>2</sub>O.

5

The purified samples from the second step PCR reaction were digested with NcoI/HindIII using one of two standardized digestion conditions. For Geneclean II purified samples, 10 ul of DNA were digested in a 20 ul reaction with 7.5 U each of NcoI/HindIII for two hours at 37°C, and gel purified on a 1.1% TAE agarose gel again with Geneclean II. Ligation-ready samples were resuspended in 10 ul dH<sub>2</sub>O. For pMON32322, 20 ul of sample was digested in a 50 ul reaction volume with 20U each of NcoI and HindIII for 3 hour at 37°C. 0.1 volume 3M NaOAc (pH 5.5) and 2.5 volume of EtOH were added, mixed, and stored at -20°C overnight. The DNA was recovered by pelleting for 20 minutes at 13,000 rpm @ 4°C in a Sigma Mk 202 microfuge. The DNA pellet was rinsed with chilled 70% EtOH, lyophilized, and resuspended in 10 ul dH<sub>2</sub>O.

### EXAMPLE 3

25 An alternate approach was used to construct pMON32320 (39/40 breakpoint, fifteen amino acid linker), pMON32323 (65/66 breakpoint, fifteen AA linker), and pMON32324 (65/66 breakpoint, ten amino acid linker). New primers (L15C, L15D, L15E) were designed to incorporate BamHI  
30 restriction site in the primer that was inframe to allow cloning into the BamHI site and maintain the proper reading frame. PCR reaction conditions for the first step were performed identically to that described for pMON32322, except that the following set of primer pairs  
35 were used: 65For/L15D and 65Rev/L15E (pMON32324); 39For/L15D and 39Rev/L15C (pMON32320); and 65For/L15D and 65Rev/L15C (pMON32323). The PCR reaction products

were purified using a Wizard PCR Clean Up kit as described, and eluted in 50 ul dH<sub>2</sub>O. Samples were digested with either NcoI/BamHI (39For/L15D and 65For/L15D) or BamHI/HindIII (39Rev/L15C, 65Rev/L15C, and 65Rev/L15E). Restriction digests were performed as follows: 10 ul of purified PCR reaction products, 3 ul of 10X universal restriction buffer, 15 U of either NcoI or HindIII, 15 U of BamHI, in a final reaction volume of 30 ul. Reactions were incubated for 90 minutes at 37°C, and the PCR products gel purified on a 1.1% TAE agarose gel using Geneclean II. Ligation-ready DNA was resuspended in 10 ul dH<sub>2</sub>O.

Inserts were ligated to NcoI/ HindIII digested pMON3977 (BHK mammalian expression vector) that had been treated with shrimp alkaline phosphatase (SAP) either in a three way (pMON32320, pMON32323, or pMON32324) or a two way (pMON32321, pMON32322, pMON32325, pMON32326, pMON32327 and pMON32328) ligation reaction as follows: 2.5 ul of insert (2 ul of each primer pair amplicon for pMON32320, pMON32323, and pMON32324) was added to 50 ng of vector in a ten ul reaction using standard ligation conditions. Two ul of each reaction was transformed with 100 ul of chemically competent DH5α cells (Gibco/BRL) following the manufacturers suggested protocol. Twenty five ul and 200 ul aliquots were plated out on LB plates containing 50 ug/mL ampicillin and incubated overnight. Isolated colonies were picked and DNA prepared from 50 mL overnight cultures using Qiagen DNA midiprep kits. DNA was quantitated by absorbance at A260/A280, and verified for correct insert size by agarose gel electrophoresis following digestion of 1 ug template with NcoI/HindIII restriction endonucleases. Samples containing inserts of the predicted size were sequenced in both orientations using vector-specific primers using an automated fluorescent DNA sequencer model 373A (Perkin Elmer ABI). Sequencing

reactions were done in 20 ul reaction volumes using a Perkin Elmer model 480 DNA thermal cycler as follows: one ug of template, 3.2 pmole primer, 1 ul DMSO, 9.5 ul Taq terminator dyedexoxy premix ( Perkin Elmer ABI) were  
5 combined, and subjected to 25 cycles of sequencing amplification as follows: 30 seconds at 94°C, 15 second annealing at 50°C, followed by a four minute extension cycle at 60°C. Samples were purified using Centri-Sep spin columns (Princeton Separations) following the  
10 manufacturers suggested protocol, lyophilized, and submitted for sequence analysis. Samples containing the predicted amino acid sequence were selected for analysis and assigned pMONnumbers.

15

EXAMPLE 4

A similar approach used to construct pMON32320, pMON32323, and pMON32324 was utilized to introduce the second linker type (SerGlyGlySerGly)X where x = 2 or 3,  
20 into two sequence rearranged flt3 receptor agonists containing the 39/40 breakpoint (pMON32348 and 32350). The primer pairs were as follows: for pMON32348 the combinations of 339For2/339Rev3 and 339Rev2/339-10For3 and for pMON32350 the combinations of 339For2/339Rev3  
25 and 339Rev2/339-15For3 were used to create three PCR amplification products. Each PCR amplification was set up as follows: to 100 ng of heat denatured pMON32320, 50 pmole of each primer pair, 10 ul of 5X Buffer B, 5 U of Taq polymerase and dH<sub>2</sub>O was added to a final volume of  
30 45 ul. Reactions were pre-incubated as described before. Fifteen amplification cycles were done under the following conditions: heat denature at 94°C, one minute, followed by a two minute annealing step at 70°C, and a three minute extension at 72°C. After the last  
35 cycle, a single 72 deg extension step of 7 minutes was done. The PCR amplification products of primer pairs 339For2/339Rev3, 339Rev2/339-10For3, and 339Rev2/339-15For2 were purified using a Wizard PCR Clean Up kit

(Promega), and eluted in 50 ul dH<sub>2</sub>O. NcoI/BamHI digests for the 339For2/339Rev3 primer pair as follows: 8 ul of DNA template was mixed with 2 ul universal restriction buffer and 10 U each of NcoI and BamHI in a 20 ul reaction volume, and incubated for 90 minutes at 37°C. The digestion products was purified using the Geneclean II direct purification protocol, and ligation ready DNA resuspended in 10 ul dH<sub>2</sub>O. The restriction digests and subsequent purification for the 339Rev2/339-10For3 and 339Rev2/339-15For2 amplification products were done identically as described for the 339For2/339Rev3 amplicon, except that 10 U of HindIII was substituted for NcoI. Standard ligations were done by adding to 50 ng NcoI/HindIII/SAP-treated, gel purified pMON3977, 0.5 ul 339For2/Rev3 amplicon, 1 ul of either 339Rev2/339-10For3 (pMON32348) or 339Rev2/339-15For3 (pMON32350) amplicons, 5U T4 DNA ligase, and 1 ul 10 X ligase buffer in a 10 ul reaction volume for 60 minutes at ambient temperature. Subsequent steps leading to final DNA sequence confirmation were done as described above.

#### EXAMPLE 5

A third type of linker, with a variable (GlyGlyGlySer)<sub>X</sub> repeat motif, was incorporated into another set of sequence rearranged flt3 receptor agonists from modularly constructed templates. These linker lengths were;

6 AA linker (GlyGlyGlySerGlyGly SEQ ID NO:51),  
7 AA linker (GlyGlyGlySerGlyGlyGly SEQ ID NO:52),  
10 AA linker (GlyGlyGlySerGlyGlyGlySerGlyGly SEQ ID NO:53),  
13 AA linker (GlyGlyGlySerGlyGlyGlySerGlyGlyGlySerGly SEQ ID NO:54),

15 AA linker  
(GlyGlyGlySerGlyGlyGlySerGlyGlyGlySerGlyGlyGly SEQ ID  
NO:55); and  
21 AA linker  
5 (GlyGlyGlySerGlyGlyGlySerGlyGlyGlySerGlyGlyGlySerGlyGly  
GlySerGly SEQ ID NO:56) amino acid residues. These modular  
templates, each comprising a dimer of hflt3 ligand  
separated by a BamHI-containing linker of unique length,  
were constructed as follows. Six intermediate PLASMID  
10 templates, FL3N, FL7N, FL11N, FL3C, FL4C, and FL10C,  
were constructed by PCR using paired primers and  
pMON30238 as template using cycling conditions similar  
to those employed for pMON32322. Per reaction, 50 pmole  
of each primer was added to 100 ng of heat-denatured  
15 template and the reactions assembled as described for  
pMON32322. Cycle conditions were as follows: seven  
cycles of 94°C, one minute; two minutes at 65°C, and 2.5  
minutes at 72°C; followed by ten cycles of one minute at  
94°C, two minutes at 70°C, and 2.5 minutes at 72°C. A  
20 single seven minute extension at 72°C completed the  
cycling reactions. The primer pairs used to construct  
each intermediate were; N-term/FLN3 (FL3N); N-term/FLN7  
(FL7N); N-term/FLN11 (FL11N); C term/FLC3 (FL3C); C-  
term/FLC4 (FL4C); and C-term/FLC10 (FL10C). The PCR  
25 amplification products were purified with Wizard PCR  
Clean Up kits (Promega) and eluted in 50 ul dH<sub>2</sub>O.  
Purified DNA for the first subset, FL3N, FL7N, and  
FL11N, were digested with NcoI/BamHI, gel purified as  
described previously, and ligated to NcoI/BamHI/Sap-  
30 treated pSE420 vector DNA (Invitrogen). Intermediate  
templates of the second subset, FL3C, FL4C, and FL10C,  
were constructed in an identical manner except HindIII  
was utilized instead of NcoI. Subsequent steps leading  
to final DNA sequence confirmation were done as  
35 described above.

EXAMPLE 6

To make the next six templates, the two subsets of intermediates in pSE420 were digested with either NcoI/BamHI (FL3N, FL7N, FL11N-subset 1) or BamHI/HindIII (FL3C, FL4C, FL10C-subset 2) and gel purified using Geneclean II as described previously. One intermediate amplicon from each subset were ligated to NcoI/HindIII/SAP-treated pMON3977 per reaction and transformed in DH5 $\alpha$  cells as described previously using the following combinations to generate specific linker lengths: six AA linker (FL3N and FL3C), seven AA linker (FL3N and FL4C), ten AA linker (FL7N and FL3C), thirteen AA linker (FL3N and FL10C), fifteen AA linker (FL11N and FL4C), and 21 AA linker (FL11N and FL10C). DNA was prepared 50 mL overnight cultures from single colonies from each of the six combination as described above, analyzed for correct insert size by NcoI/HindIII restriction analysis, and used as template. Primer pairs 39For/39Rev (39/40 breakpoint); 65For/65Rev (65/66 breakpoint) and 89For/89Rev (89/90 breakpoint) were used to PCR amplify each templates as described for pMON32322, except 75 pmole of each primer was used. Amplification conditions were modified as follows: six cycles of 94°C for one minute, 2 minutes at 70°C, 2.5 minutes at 72°C; followed by nine cycles of 94°C for one minute, and three minutes at 72°C. After the last cycle, a final extension of six minutes at 72°C allowed ample time for full extension of products. Samples were purified using a Wizard PCR Clean Up kit as described, and double digested with NcoI/HindIII. These amplification products were purified again using a Wizard PCR Clean Up kit. In addition, all six different linker length molecules for the 39/40 breakpoint were cloned into NcoI/HindIII/SAP-treated pMON3977 as single proteins (pMON32365, pMON32366, pMON32367, pMON32368, pMON32369 and 32370). Subsequent steps leading to final DNA sequence confirmation were done as described above.

## EXAMPLE 7

Additional sequence rearranged Flt3 ligands were  
5 constructed using the dimer template intermediates  
previously described. For sequence rearranged Flt3  
ligands having the fifteen amino acid linker  
(GlyGlyGlySer)<sub>3</sub>GlyGlyGly SEQ ID NO:55, the dimer  
intermediates Flt4C.seq and Flt11N.seq were used as the  
10 template in the PCR reaction. Five new breakpoints  
corresponding to Flt3 ligand amino acid residues 28/29,  
34/35, 62/63, 94/95, and 98/99, were constructed using a  
PCR based approach using a PCR Optimizer kit  
(Invitrogen) and the following primer pairs;  
15 FL29For/FL29Rev, FL35For/FL35Rev, FL63For/FL63Rev,  
FL95For/FL95Rev, FL99For/FL99Rev. Amplification  
conditions were as follows: seven cycles of 94°C for 1',  
62°C for 2', and 2.5' at 70°C; twelve cycles of 94°C for  
1', 68°C for 2', and 70°C for 2.5'; followed by a final  
20 cycle of 7' at 72°C. PCR products corresponding to the  
predicted insert size were digested to completion with  
NcoI and HindIII, and gel purified as described  
previously using Gene Clean II (Bio 101) following the  
manufacturers suggested protocol. Samples were  
25 resuspended in 10 ul final volume with dH<sub>2</sub>O. Inserts  
were cloned as single genes into the mammalian  
expression vector pMON3977 (NcoI/HindIII/SAP treated)  
and designated pMON35712, pMON35713, pMON35714,  
pMON35715, pMON35716, pMON35717, pMON35718 respectively.

30

Additional techniques for the construction of the  
variant genes, recombinant protein expression, protein  
35 purification, protein characterization, biological  
activity determination can be found in WO 94/12639, WO  
94/12638, WO 95/20976, WO 95/21197, WO 95/20977, WO

95/21254 and WO 96/23888 which are hereby incorporated by reference in their entirety.

5 All references, patents or applications cited herein are incorporated by reference in their entirety as if written herein.

10 Various other examples will be apparent to the person skilled in the art after reading the present disclosure without departing from the spirit and scope of the invention. It is intended that all such other examples be included within the scope of the appended claims.

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## SEQUENCE LISTING

## (1) GENERAL INFORMATION

- (i) APPLICANT: G.D. Searle Corporate Patent Department
- (ii) TITLE OF THE INVENTION: Novel *flt3* Receptor Agonists
- (iii) NUMBER OF SEQUENCES: 151
- (iv) CORRESPONDENCE ADDRESS:
  - (A) ADDRESSEE: G. D. Searle Corporate Patent Department
  - (B) STREET: P.O. Box 55110
  - (C) CITY: Chicago
  - (D) STATE: IL
  - (E) COUNTRY: USA
  - (F) ZIP: 60680
- (v) COMPUTER READABLE FORM:
  - (A) MEDIUM TYPE: Diskette
  - (B) COMPUTER: IBM Compatible
  - (C) OPERATING SYSTEM: DOS
  - (D) SOFTWARE: FastSEQ for Windows Version 2.0
- (vi) CURRENT APPLICATION DATA:
  - (A) APPLICATION NUMBER:
  - (B) FILING DATE: 21-OCT-1997
  - (C) CLASSIFICATION:
- (vii) PRIOR APPLICATION DATA:
  - (A) APPLICATION NUMBER: 60/030,094
  - (B) FILING DATE: 25-OCT-1996
- (viii) ATTORNEY/AGENT INFORMATION:
  - (A) NAME: Bennett, Dennis A
  - (B) REGISTRATION NUMBER: 34,547
  - (C) REFERENCE/DOCKET NUMBER: C-2993/2
- (ix) TELECOMMUNICATION INFORMATION:
  - (A) TELEPHONE: 314-737-6986
  - (B) TELEFAX: 314-737-6972
  - (C) TELEX:

## (2) INFORMATION FOR SEQ ID NO:1:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 135 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Thr | Gln | Asp | Cys | Ser | Phe | Gln | His | Ser | Pro | Ile | Ser | Ser | Asp | Phe |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |
| Ala | Val | Lys | Ile | Arg | Glu | Leu | Ser | Asp | Tyr | Leu | Leu | Gln | Asp | Tyr | Pro |
|     |     | 20  |     |     |     |     |     | 25  |     |     |     |     | 30  |     |     |
| Val | Thr | Val | Ala | Ser | Asn | Leu | Gln | Asp | Glu | Glu | Leu | Cys | Gly | Ala | Leu |
|     |     | 35  |     |     |     | 40  |     |     |     |     |     | 45  |     |     |     |
| Trp | Arg | Leu | Val | Leu | Ala | Gln | Arg | Trp | Met | Glu | Arg | Leu | Lys | Thr | Val |
|     | 50  |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |     |
| Ala | Gly | Ser | Lys | Met | Gln | Gly | Leu | Leu | Glu | Arg | Val | Asn | Thr | Glu | Ile |
| 65  |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |     |
| His | Phe | Val | Thr | Lys | Cys | Ala | Phe | Gln | Pro | Pro | Pro | Ser | Cys | Leu | Arg |
|     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |     |
| Phe | Val | Gln | Thr | Asn | Ile | Ser | Arg | Leu | Leu | Gln | Glu | Thr | Ser | Glu | Gln |
|     |     | 100 |     |     |     |     |     | 105 |     |     |     |     | 110 |     |     |
| Leu | Val | Ala | Leu | Lys | Pro | Trp | Ile | Thr | Arg | Gln | Asn | Phe | Ser | Arg | Cys |
|     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |
| Leu | Glu | Leu | Gln | Cys | Gln | Pro |     |     |     |     |     |     |     |     |     |

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## (2) INFORMATION FOR SEQ ID NO:2:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 140 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

```

Ala Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe
 1          5          10          15
Ala Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro
 20          25          30
Val Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu Cys Gly Gly Leu
 35          40          45
Trp Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg Leu Lys Thr Val
 50          55          60
Ala Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile
 65          70          75          80
His Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Ser Cys Leu Arg
 85          90          95
Phe Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln
100          105          110
Leu Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys
115          120          125
Leu Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu
130          135          140

```

## (2) INFORMATION FOR SEQ ID NO:3:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 122 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

```

Ala Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe
 1          5          10          15
Ala Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro
 20          25          30
Val Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu Cys Gly Gly Leu
 35          40          45
Trp Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg Leu Lys Thr Val
 50          55          60
Ala Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile
 65          70          75          80
His Phe Val Thr Lys Cys Ala Phe Gln Glu Thr Ser Glu Gln Leu Val
 85          90          95
Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu Glu
100          105          110
Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu
115          120

```

## (2) INFORMATION FOR SEQ ID NO:4:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 135 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

```

Gly Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe
 1          5          10          15
Ala Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro

```

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```

      20      25      30
Val Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu Cys Gly Gly Leu
      35      40      45
Trp Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg Leu Lys Thr Val
      50      55      60
Ala Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile
      65      70      75      80
His Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Pro Ser Cys Leu Arg
      85      90      95
Phe Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln
      100      105      110
Leu Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys
      115      120      125
Leu Glu Leu Gln Cys Gln Pro
      130      135

```

## (2) INFORMATION FOR SEQ ID NO:5:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 140 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

```

Gly Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe
 1      5      10      15
Ala Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro
      20      25      30
Val Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu Cys Gly Gly Leu
      35      40      45
Trp Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg Leu Lys Thr Val
      50      55      60
Ala Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile
      65      70      75      80
His Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Pro Ser Cys Leu Arg
      85      90      95
Phe Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln
      100      105      110
Leu Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys
      115      120      125
Leu Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu
      130      135      140

```

## (2) INFORMATION FOR SEQ ID NO:6:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 135 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

```

Ala Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe
 1      5      10      15
Ala Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro
      20      25      30
Val Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu Cys Gly Gly Leu
      35      40      45
Trp Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg Leu Lys Thr Val
      50      55      60
Ala Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile
      65      70      75      80
His Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Pro Ser Cys Leu Arg
      85      90      95
Phe Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln
      100      105      110
Leu Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys
      115      120      125
Leu Glu Leu Gln Cys Gln Pro
      130      135

```

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## (2) INFORMATION FOR SEQ ID NO:7:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 140 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

```

Ala Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe
 1      5      10      15
Ala Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro
 20      25      30
Val Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu Cys Gly Gly Leu
 35      40      45
Trp Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg Leu Lys Thr Val
 50      55      60
Ala Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile
 65      70      75      80
His Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Pro Ser Cys Leu Arg
 85      90      95
Phe Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln
100      105      110
Leu Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys
115      120      125
Leu Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu
130      135      140

```

## (2) INFORMATION FOR SEQ ID NO:8:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 155 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

```

Ala Asp Glu Glu Leu Cys Gly Gly Leu Trp Arg Leu Val Leu Ala Gln
 1      5      10      15
Arg Trp Met Glu Arg Leu Lys Thr Val Ala Gly Ser Lys Met Gln Gly
 20      25      30
Leu Leu Glu Arg Val Asn Thr Glu Ile His Phe Val Thr Lys Cys Ala
 35      40      45
Phe Gln Pro Pro Pro Ser Cys Leu Arg Phe Val Gln Thr Asn Ile Ser
 50      55      60
Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu Val Ala Leu Lys Pro Trp
 65      70      75      80
Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu Glu Leu Gln Cys Gln Pro
 85      90      95
Asp Ser Ser Thr Leu Ser Gly Gly Asn Gly Ser Gly Gly Asn Gly Ser
100      105      110
Gly Gly Asn Gly Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser
115      120      125
Ser Asp Phe Ala Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln
130      135      140
Asp Tyr Pro Val Thr Val Ala Ser Asn Leu Gln
145      150      155

```

## (2) INFORMATION FOR SEQ ID NO:9:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 150 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

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```

Ala Asp Glu Glu Leu Cys Gly Gly Leu Trp Arg Leu Val Leu Ala Gln
 1      5      10      15
Arg Trp Met Glu Arg Leu Lys Thr Val Ala Gly Ser Lys Met Gln Gly
      20      25      30
Leu Leu Glu Arg Val Asn Thr Glu Ile His Phe Val Thr Lys Cys Ala
      35      40      45
Phe Gln Pro Pro Pro Ser Cys Leu Arg Phe Val Gln Thr Asn Ile Ser
      50      55      60
Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu Val Ala Leu Lys Pro Trp
65      70      75      80
Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu Glu Leu Gln Cys Gln Pro
      85      90      95
Asp Ser Ser Thr Leu Ser Gly Gly Asn Gly Ser Gly Gly Asn Gly Thr
      100      105      110
Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala Val
      115      120      125
Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val Thr
130      135      140
Val Ala Ser Asn Leu Gln
145      150

```

## (2) INFORMATION FOR SEQ ID NO:10:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 145 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

```

Ala Asp Glu Glu Leu Cys Gly Gly Leu Trp Arg Leu Val Leu Ala Gln
 1      5      10      15
Arg Trp Met Glu Arg Leu Lys Thr Val Ala Gly Ser Lys Met Gln Gly
      20      25      30
Leu Leu Glu Arg Val Asn Thr Glu Ile His Phe Val Thr Lys Cys Ala
      35      40      45
Phe Gln Pro Pro Pro Ser Cys Leu Arg Phe Val Gln Thr Asn Ile Ser
      50      55      60
Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu Val Ala Leu Lys Pro Trp
65      70      75      80
Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu Glu Leu Gln Cys Gln Pro
      85      90      95
Asp Ser Ser Thr Leu Ser Gly Gly Asn Gly Thr Gln Asp Cys Ser Phe
      100      105      110
Gln His Ser Pro Ile Ser Ser Asp Phe Ala Val Lys Ile Arg Glu Leu
      115      120      125
Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val Thr Val Ala Ser Asn Leu
130      135      140
Gln
145

```

## (2) INFORMATION FOR SEQ ID NO:11:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 155 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

```

Ala Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile His
 1      5      10      15
Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Pro Ser Cys Leu Arg Phe
      20      25      30
Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu
      35      40      45
Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu
      50      55      60
Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Ser Gly Gly Asn Gly
65      70      75      80
Ser Gly Gly Asn Gly Ser Gly Gly Asn Gly Thr Gln Asp Cys Ser Phe

```

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```

      85      90      95
Gln His Ser Pro Ile Ser Ser Asp Phe Ala Val Lys Ile Arg Glu Leu
      100      105      110
Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val Thr Val Ala Ser Asn Leu
      115      120      125
Gln Asp Glu Glu Leu Cys Gly Gly Leu Trp Arg Leu Val Leu Ala Gln
      130      135      140
Arg Trp Met Glu Arg Leu Lys Thr Val Ala Gly
      145      150      155

```

## (2) INFORMATION FOR SEQ ID NO:12:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 150 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

```

Ala Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile His
 1      5      10      15
Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Ser Cys Leu Arg Phe
 20      25      30
Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu
 35      40      45
Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu
 50      55      60
Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Ser Gly Gly Asn Gly
 65      70      75      80
Ser Gly Gly Asn Gly Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile
 85      90      95
Ser Ser Asp Phe Ala Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu
 100      105      110
Gln Asp Tyr Pro Val Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu
 115      120      125
Cys Gly Gly Leu Trp Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg
 130      135      140
Leu Lys Thr Val Ala Gly
 145      150

```

## (2) INFORMATION FOR SEQ ID NO:13:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 145 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

```

Ala Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile His
 1      5      10      15
Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Pro Ser Cys Leu Arg Phe
 20      25      30
Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu
 35      40      45
Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu
 50      55      60
Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Ser Gly Gly Asn Gly
 65      70      75      80
Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala
 85      90      95
Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val
 100      105      110
Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu Cys Gly Gly Leu Trp
 115      120      125
Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg Leu Lys Thr Val Ala
 130      135      140
Gly
 145

```

## (2) INFORMATION FOR SEQ ID NO:14:

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## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 155 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Pro | Pro | Ser | Cys | Leu | Arg | Phe | Val | Gln | Thr | Asn | Ile | Ser | Arg | Leu |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |
| Leu | Gln | Glu | Thr | Ser | Glu | Gln | Leu | Val | Ala | Leu | Lys | Pro | Trp | Ile | Thr |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |
| Arg | Gln | Asn | Phe | Ser | Arg | Cys | Leu | Glu | Leu | Gln | Cys | Gln | Pro | Asp | Ser |
|     |     | 35  |     |     |     | 40  |     |     |     |     | 45  |     |     |     |     |
| Ser | Thr | Leu | Ser | Gly | Gly | Asn | Gly | Ser | Gly | Gly | Asn | Gly | Ser | Gly | Gly |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |
| Asn | Gly | Thr | Gln | Asp | Cys | Ser | Phe | Gln | His | Ser | Pro | Ile | Ser | Ser | Asp |
| 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     | 80  |     |
| Phe | Ala | Val | Lys | Ile | Arg | Glu | Leu | Ser | Asp | Tyr | Leu | Leu | Gln | Asp | Tyr |
|     |     |     | 85  |     |     |     |     |     | 90  |     |     |     | 95  |     |     |
| Pro | Val | Thr | Val | Ala | Ser | Asn | Leu | Gln | Asp | Glu | Glu | Leu | Cys | Gly | Gly |
|     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |
| Leu | Trp | Arg | Leu | Val | Leu | Ala | Gln | Arg | Trp | Met | Glu | Arg | Leu | Lys | Thr |
|     |     | 115 |     |     |     | 120 |     |     |     |     |     | 125 |     |     |     |
| Val | Ala | Gly | Ser | Lys | Met | Gln | Gly | Leu | Leu | Glu | Arg | Val | Asn | Thr | Glu |
|     | 130 |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |
| Ile | His | Phe | Val | Thr | Lys | Cys | Ala | Phe | Gln | Pro |     |     |     |     |     |
| 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     |     |

## (2) INFORMATION FOR SEQ ID NO:15:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 150 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Pro | Pro | Ser | Cys | Leu | Arg | Phe | Val | Gln | Thr | Asn | Ile | Ser | Arg | Leu |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |
| Leu | Gln | Glu | Thr | Ser | Glu | Gln | Leu | Val | Ala | Leu | Lys | Pro | Trp | Ile | Thr |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |
| Arg | Gln | Asn | Phe | Ser | Arg | Cys | Leu | Glu | Leu | Gln | Cys | Gln | Pro | Asp | Ser |
|     |     | 35  |     |     |     | 40  |     |     |     |     | 45  |     |     |     |     |
| Ser | Thr | Leu | Ser | Gly | Gly | Asn | Gly | Ser | Gly | Gly | Asn | Gly | Thr | Gln | Asp |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |
| Cys | Ser | Phe | Gln | His | Ser | Pro | Ile | Ser | Ser | Asp | Phe | Ala | Val | Lys | Ile |
| 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     | 80  |     |
| Arg | Glu | Leu | Ser | Asp | Tyr | Leu | Leu | Gln | Asp | Tyr | Pro | Val | Thr | Val | Ala |
|     |     |     | 85  |     |     |     |     |     | 90  |     |     |     | 95  |     |     |
| Ser | Asn | Leu | Gln | Asp | Glu | Glu | Leu | Cys | Gly | Gly | Leu | Trp | Arg | Leu | Val |
|     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |
| Leu | Ala | Gln | Arg | Trp | Met | Glu | Arg | Leu | Lys | Thr | Val | Ala | Gly | Ser | Lys |
|     |     | 115 |     |     |     | 120 |     |     |     |     | 125 |     |     |     |     |
| Met | Gln | Gly | Leu | Leu | Glu | Arg | Val | Asn | Thr | Glu | Ile | His | Phe | Val | Thr |
|     | 130 |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |
| Lys | Cys | Ala | Phe | Gln | Pro |     |     |     |     |     |     |     |     |     |     |
| 145 |     |     |     |     | 150 |     |     |     |     |     |     |     |     |     |     |

## (2) INFORMATION FOR SEQ ID NO:16:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 145 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

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```

Ala Pro Pro Ser Cys Leu Arg Phe Val Gln Thr Asn Ile Ser Arg Leu
 1      5      10      15
Leu Gln Glu Thr Ser Glu Gln Leu Val Ala Leu Lys Pro Trp Ile Thr
      20      25      30
Arg Gln Asn Phe Ser Arg Cys Leu Glu Leu Gln Cys Gln Pro Asp Ser
      35      40      45
Ser Thr Leu Ser Gly Gly Asn Gly Thr Gln Asp Cys Ser Phe Gln His
 50      55      60
Ser Pro Ile Ser Ser Asp Phe Ala Val Lys Ile Arg Glu Leu Ser Asp
65      70      75      80
Tyr Leu Leu Gln Asp Tyr Pro Val Thr Val Ala Ser Asn Leu Gln Asp
      85      90      95
Glu Glu Leu Cys Gly Gly Leu Trp Arg Leu Val Leu Ala Gln Arg Trp
      100      105      110
Met Glu Arg Leu Lys Thr Val Ala Gly Ser Lys Met Gln Gly Leu Leu
      115      120      125
Glu Arg Val Asn Thr Glu Ile His Phe Val Thr Lys Cys Ala Phe Gln
130      135      140
Pro
145

```

## (2) INFORMATION FOR SEQ ID NO:17:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 155 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

```

Ala Asp Glu Glu Leu Cys Gly Gly Leu Trp Arg Leu Val Leu Ala Gln
 1      5      10      15
Arg Trp Met Glu Arg Leu Lys Thr Val Ala Gly Ser Lys Met Gln Gly
      20      25      30
Leu Leu Glu Arg Val Asn Thr Glu Ile His Phe Val Thr Lys Cys Ala
      35      40      45
Phe Gln Pro Pro Pro Ser Cys Leu Arg Phe Val Gln Thr Asn Ile Ser
 50      55      60
Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu Val Ala Leu Lys Pro Trp
65      70      75      80
Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu Glu Leu Gln Cys Gln Pro
      85      90      95
Asp Ser Ser Thr Leu Ser Gly Gly Ser Gly Ser Gly Gly Ser Gly Ser
      100      105      110
Gly Gly Ser Gly Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser
      115      120      125
Ser Asp Phe Ala Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln
130      135      140
Asp Tyr Pro Val Thr Val Ala Ser Asn Leu Gln
145      150      155

```

## (2) INFORMATION FOR SEQ ID NO:18:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 150 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

```

Ala Asp Glu Glu Leu Cys Gly Gly Leu Trp Arg Leu Val Leu Ala Gln
 1      5      10      15
Arg Trp Met Glu Arg Leu Lys Thr Val Ala Gly Ser Lys Met Gln Gly
      20      25      30
Leu Leu Glu Arg Val Asn Thr Glu Ile His Phe Val Thr Lys Cys Ala
      35      40      45
Phe Gln Pro Pro Pro Ser Cys Leu Arg Phe Val Gln Thr Asn Ile Ser
 50      55      60
Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu Val Ala Leu Lys Pro Trp
65      70      75      80
Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu Glu Leu Gln Cys Gln Pro

```

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```

      85      90      95
Asp Ser Ser Thr Leu Ser Gly Gly Ser Gly Ser Gly Gly Ser Ser Thr
      100      105      110
Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala Val
      115      120      125
Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val Thr
      130      135      140
Val Ala Ser Asn Leu Gln
      145      150

```

## (2) INFORMATION FOR SEQ ID NO:19:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 145 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

```

Met Ala Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp
 1      5      10      15
Phe Ala Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr
      20      25      30
Pro Val Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu Cys Gly Gly
      35      40      45
Leu Trp Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg Leu Lys Thr
      50      55      60
Val Ala Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu
      65      70      75      80
Ile His Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Pro Ser Cys Leu
      85      90      95
Arg Phe Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu
      100      105      110
Gln Leu Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg
      115      120      125
Cys Leu Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Gly Gly Gly
      130      135      140
Ser
      145

```

## (2) INFORMATION FOR SEQ ID NO:20:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 143 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

```

Gly Ser Gly Gly Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser
 1      5      10      15
Ser Asp Phe Ala Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln
      20      25      30
Asp Tyr Pro Val Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu Cys
      35      40      45
Gly Gly Leu Trp Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg Leu
      50      55      60
Lys Thr Val Ala Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn
      65      70      75      80
Thr Glu Ile His Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Pro Ser
      85      90      95
Cys Leu Arg Phe Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr
      100      105      110
Ser Glu Gln Leu Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe
      115      120      125
Ser Arg Cys Leu Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu
      130      135      140

```

## (2) INFORMATION FOR SEQ ID NO:21:

## (i) SEQUENCE CHARACTERISTICS:

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(A) LENGTH: 149 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

```

Met Ala Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp
 1           5           10          15
Phe Ala Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr
          20          25          30
Pro Val Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu Cys Gly Gly
          35          40          45
Leu Trp Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg Leu Lys Thr
          50          55          60
Val Ala Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu
          65          70          75          80
Ile His Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Pro Ser Cys Leu
          85          90          95
Arg Phe Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu
          100         105         110
Gln Leu Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg
          115         120         125
Cys Leu Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Gly Gly Gly
          130         135         140
Ser Gly Gly Gly Ser
145

```

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 144 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

```

Gly Ser Gly Gly Gly Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile
 1           5           10          15
Ser Ser Asp Phe Ala Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu
          20          25          30
Gln Asp Tyr Pro Val Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu
          35          40          45
Cys Gly Gly Leu Trp Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg
          50          55          60
Leu Lys Thr Val Ala Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val
          65          70          75          80
Asn Thr Glu Ile His Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Pro
          85          90          95
Ser Cys Leu Arg Phe Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu
          100         105         110
Thr Ser Glu Gln Leu Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn
          115         120         125
Phe Ser Arg Cys Leu Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu
          130         135         140

```

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 153 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

```

Met Ala Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp
 1           5           10          15
Phe Ala Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr
          20          25          30

```

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```

Pro Val Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu Cys Gly Gly
      35          40          45
Leu Trp Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg Leu Lys Thr
      50          55          60
Val Ala Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu
      65          70          75          80
Ile His Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Pro Ser Cys Leu
      85          90          95
Arg Phe Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu
      100         105         110
Gln Leu Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg
      115         120         125
Cys Leu Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Gly Gly Gly
      130         135         140
Ser Gly Gly Gly Ser Gly Gly Gly Ser
      145         150

```

## (2) INFORMATION FOR SEQ ID NO:24:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 150 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

```

Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Thr Gln Asp Cys Ser
  1      5      10      15
Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala Val Lys Ile Arg Glu
      20      25      30
Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val Thr Val Ala Ser Asn
      35      40      45
Leu Gln Asp Glu Glu Leu Cys Gly Gly Leu Trp Arg Leu Val Leu Ala
      50      55      60
Gln Arg Trp Met Glu Arg Leu Lys Thr Val Ala Gly Ser Lys Met Gln
      65      70      75      80
Gly Leu Leu Glu Arg Val Asn Thr Glu Ile His Phe Val Thr Lys Cys
      85      90      95
Ala Phe Gln Pro Pro Pro Ser Cys Leu Arg Phe Val Gln Thr Asn Ile
      100     105     110
Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu Val Ala Leu Lys Pro
      115     120     125
Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu Glu Leu Gln Cys Gln
      130     135     140
Pro Asp Ser Ser Thr Leu
      145     150

```

## (2) INFORMATION FOR SEQ ID NO:25:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 146 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

```

Ala Asp Glu Glu Leu Cys Gly Gly Leu Trp Arg Leu Val Leu Ala Gln
  1      5      10      15
Arg Trp Met Glu Arg Leu Lys Thr Val Ala Gly Ser Lys Met Gln Gly
      20      25      30
Leu Leu Glu Arg Val Asn Thr Glu Ile His Phe Val Thr Lys Cys Ala
      35      40      45
Phe Gln Pro Pro Pro Ser Cys Leu Arg Phe Val Gln Thr Asn Ile Ser
      50      55      60
Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu Val Ala Leu Lys Pro Trp
      65      70      75      80
Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu Glu Leu Gln Cys Gln Pro
      85      90      95
Asp Ser Ser Thr Leu Gly Gly Gly Ser Gly Gly Thr Gln Asp Cys Ser
      100     105     110
Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala Val Lys Ile Arg Glu

```

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```

          115          120          125
Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val Thr Val Ala Ser Asn
   130          135          140
Leu Gln
145

```

## (2) INFORMATION FOR SEQ ID NO:26:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 147 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

```

Ala Asp Glu Glu Leu Cys Gly Gly Leu Trp Arg Leu Val Leu Ala Gln
 1          5          10          15
Arg Trp Met Glu Arg Leu Lys Thr Val Ala Gly Ser Lys Met Gln Gly
   20          25          30
Leu Leu Glu Arg Val Asn Thr Glu Ile His Phe Val Thr Lys Cys Ala
   35          40          45
Phe Gln Pro Pro Pro Ser Cys Leu Arg Phe Val Gln Thr Asn Ile Ser
   50          55          60
Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu Val Ala Leu Lys Pro Trp
 65          70          75          80
Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu Glu Leu Gln Cys Gln Pro
   85          90          95
Asp Ser Ser Thr Leu Gly Gly Gly Ser Gly Gly Gly Thr Gln Asp Cys
   100          105          110
Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala Val Lys Ile Arg
   115          120          125
Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val Thr Val Ala Ser
   130          135          140
Asn Leu Gln
145

```

## (2) INFORMATION FOR SEQ ID NO:27:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 150 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

```

Ala Asp Glu Glu Leu Cys Gly Gly Leu Trp Arg Leu Val Leu Ala Gln
 1          5          10          15
Arg Trp Met Glu Arg Leu Lys Thr Val Ala Gly Ser Lys Met Gln Gly
   20          25          30
Leu Leu Glu Arg Val Asn Thr Glu Ile His Phe Val Thr Lys Cys Ala
   35          40          45
Phe Gln Pro Pro Pro Ser Cys Leu Arg Phe Val Gln Thr Asn Ile Ser
   50          55          60
Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu Val Ala Leu Lys Pro Trp
 65          70          75          80
Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu Glu Leu Gln Cys Gln Pro
   85          90          95
Asp Ser Ser Thr Leu Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Thr
   100          105          110
Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala Val
   115          120          125
Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val Thr
   130          135          140
Val Ala Ser Asn Leu Gln
145          150

```

## (2) INFORMATION FOR SEQ ID NO:28:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 153 amino acids  
 (B) TYPE: amino acid

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(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

```

Ala Asp Glu Glu Leu Cys Gly Gly Leu Trp Arg Leu Val Leu Ala Gln
 1          5          10          15
Arg Trp Met Glu Arg Leu Lys Thr Val Ala Gly Ser Lys Met Gln Gly
 20          25          30
Leu Leu Glu Arg Val Asn Thr Glu Ile His Phe Val Thr Lys Cys Ala
 35          40          45
Phe Gln Pro Pro Pro Ser Cys Leu Arg Phe Val Gln Thr Asn Ile Ser
 50          55          60
Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu Val Ala Leu Lys Pro Trp
 65          70          75          80
Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu Glu Leu Gln Cys Gln Pro
 85          90          95
Asp Ser Ser Thr Leu Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly
100          105          110
Ser Gly Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp
115          120          125
Phe Ala Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr
130          135          140
Pro Val Thr Val Ala Ser Asn Leu Gln
145          150

```

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 155 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

```

Ala Asp Glu Glu Leu Cys Gly Gly Leu Trp Arg Leu Val Leu Ala Gln
 1          5          10          15
Arg Trp Met Glu Arg Leu Lys Thr Val Ala Gly Ser Lys Met Gln Gly
 20          25          30
Leu Leu Glu Arg Val Asn Thr Glu Ile His Phe Val Thr Lys Cys Ala
 35          40          45
Phe Gln Pro Pro Pro Ser Cys Leu Arg Phe Val Gln Thr Asn Ile Ser
 50          55          60
Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu Val Ala Leu Lys Pro Trp
 65          70          75          80
Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu Glu Leu Gln Cys Gln Pro
 85          90          95
Asp Ser Ser Thr Leu Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly
100          105          110
Ser Gly Gly Gly Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser
115          120          125
Ser Asp Phe Ala Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln
130          135          140
Asp Tyr Pro Val Thr Val Ala Ser Asn Leu Gln
145          150          155

```

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 161 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

```

Ala Asp Glu Glu Leu Cys Gly Gly Leu Trp Arg Leu Val Leu Ala Gln
 1          5          10          15
Arg Trp Met Glu Arg Leu Lys Thr Val Ala Gly Ser Lys Met Gln Gly
 20          25          30

```

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```

Leu Leu Glu Arg Val Asn Thr Glu Ile His Phe Val Thr Lys Cys Ala
   35         40         45
Phe Gln Pro Pro Pro Ser Cys Leu Arg Phe Val Gln Thr Asn Ile Ser
   50         55         60
Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu Val Ala Leu Lys Pro Trp
   65         70         75         80
Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu Glu Leu Gln Cys Gln Pro
           85         90         95
Asp Ser Ser Thr Leu Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly
          100        105        110
Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Thr Gln Asp Cys Ser Phe
          115        120        125
Gln His Ser Pro Ile Ser Ser Asp Phe Ala Val Lys Ile Arg Glu Leu
          130        135        140
Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val Thr Val Ala Ser Asn Leu
          145        150        155        160
Gln

```

## (2) INFORMATION FOR SEQ ID NO:31:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 155 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

```

Ala Asp Tyr Pro Val Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu
  1         5         10         15
Cys Gly Gly Leu Trp Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg
  20        25        30
Leu Lys Thr Val Ala Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val
  35        40        45
Asn Thr Glu Ile His Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Pro
  50        55        60
Ser Cys Leu Arg Phe Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu
  65        70        75        80
Thr Ser Glu Gln Leu Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn
  85        90        95
Phe Ser Arg Cys Leu Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu
          100        105        110
Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Ser Gly Gly Gly Thr
          115        120        125
Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala Val
          130        135        140
Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln
          145        150        155

```

## (2) INFORMATION FOR SEQ ID NO:32:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 155 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

```

Ala Ala Ser Asn Leu Gln Asp Glu Glu Leu Cys Gly Gly Leu Trp Arg
  1         5         10         15
Leu Val Leu Ala Gln Arg Trp Met Glu Arg Leu Lys Thr Val Ala Gly
  20        25        30
Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile His Phe
  35        40        45
Val Thr Lys Cys Ala Phe Gln Pro Pro Pro Ser Cys Leu Arg Phe Val
  50        55        60
Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu Val
  65        70        75        80
Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu Glu
  85        90        95
Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Gly Gly Gly Ser Gly Gly

```

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```

      100      105      110
Gly Ser Gly Gly Ser Gly Gly Gly Thr Gln Asp Cys Ser Phe Gln
      115      120      125
His Ser Pro Ile Ser Ser Asp Phe Ala Val Lys Ile Arg Glu Leu Ser
      130      135      140
Asp Tyr Leu Leu Gln Asp Tyr Pro Val Thr Val
      145      150      155

```

## (2) INFORMATION FOR SEQ ID NO:33:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 155 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

```

Ala Val Ala Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr
 1      5      10      15
Glu Ile His Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Pro Ser Cys
      20      25      30
Leu Arg Phe Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Thr Ser
      35      40      45
Glu Gln Leu Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser
      50      55      60
Arg Cys Leu Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Gly Gly
      65      70      75      80
Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Thr Gln Asp
      85      90      95
Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala Val Lys Ile
      100      105      110
Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val Thr Val Ala
      115      120      125
Ser Asn Leu Gln Asp Glu Glu Leu Cys Gly Gly Leu Trp Arg Leu Val
      130      135      140
Leu Ala Gln Arg Trp Met Glu Arg Leu Lys Thr
      145      150      155

```

## (2) INFORMATION FOR SEQ ID NO:34:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 155 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

```

Ala Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile His
 1      5      10      15
Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Ser Cys Leu Arg Phe
      20      25      30
Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu
      35      40      45
Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu
      50      55      60
Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Gly Gly Ser Gly
      65      70      75      80
Gly Gly Ser Gly Gly Ser Gly Gly Gly Thr Gln Asp Cys Ser Phe
      85      90      95
Gln His Ser Pro Ile Ser Ser Asp Phe Ala Val Lys Ile Arg Glu Leu
      100      105      110
Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val Thr Val Ala Ser Asn Leu
      115      120      125
Gln Asp Glu Glu Leu Cys Gly Gly Leu Trp Arg Leu Val Leu Ala Gln
      130      135      140
Arg Trp Met Glu Arg Leu Lys Thr Val Ala Gly
      145      150      155

```

## (2) INFORMATION FOR SEQ ID NO:35:

## (i) SEQUENCE CHARACTERISTICS:

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(A) LENGTH: 155 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

```

Ala Pro Pro Ser Cys Leu Arg Phe Val Gln Thr Asn Ile Ser Arg Leu
 1          5          10          15
Leu Gln Glu Thr Ser Glu Gln Leu Val Ala Leu Lys Pro Trp Ile Thr
          20          25          30
Arg Gln Asn Phe Ser Arg Cys Leu Glu Leu Gln Cys Gln Pro Asp Ser
          35          40          45
Ser Thr Leu Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly
          50          55          60
Gly Gly Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp
          65          70          75          80
Phe Ala Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr
          85          90          95
Pro Val Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu Cys Gly Gly
          100          105          110
Leu Trp Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg Leu Lys Thr
          115          120          125
Val Ala Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu
          130          135          140
Ile His Phe Val Thr Lys Cys Ala Phe Gln Pro
          145          150          155

```

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 155 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

```

Ala Arg Phe Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser
 1          5          10          15
Glu Gln Leu Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser
          20          25          30
Arg Cys Leu Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Gly Gly
          35          40          45
Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Thr Gln Asp
          50          55          60
Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala Val Lys Ile
          65          70          75          80
Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val Thr Val Ala
          85          90          95
Ser Asn Leu Gln Asp Glu Glu Leu Cys Gly Gly Leu Trp Arg Leu Val
          100          105          110
Leu Ala Gln Arg Trp Met Glu Arg Leu Lys Thr Val Ala Gly Ser Lys
          115          120          125
Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile His Phe Val Thr
          130          135          140
Lys Cys Ala Phe Gln Pro Pro Ser Cys Leu
          145          150          155

```

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 155 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

```

Ala Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu Val
 1          5          10          15

```

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```

Ala Leu Lys  Pro Trp Ile Thr Arg  Gln Asn Phe Ser Arg Cys Leu Glu
      20      25
Leu Gln Cys  Gln Pro Asp Ser  Ser Thr Leu Gly Gly  Gly Ser Gly Gly
      35      40      45
Gly Ser Gly Gly Gly Ser Gly Gly Gly Thr Gln Asp Cys Ser Phe Gln
      50      55      60
His Ser Pro Ile Ser Ser Asp Phe Ala Val Lys Ile Arg Glu Leu Ser
      65      70      75      80
Asp Tyr Leu Leu Gln Asp Tyr Pro Val Thr Val Ala Ser Asn Leu Gln
      85      90      95
Asp Glu Glu Leu Cys Gly Gly Leu Trp Arg Leu Val Leu Ala Gln Arg
      100      105      110
Trp Met Glu Arg Leu Lys Thr Val Ala Gly Ser Lys Met Gln Gly Leu
      115      120      125
Leu Glu Arg Val Asn Thr Glu Ile His Phe Val Thr Lys Cys Ala Phe
      130      135      140
Gln Pro Pro Pro Ser Cys Leu Arg Phe Val Gln
      145      150      155

```

## (2) INFORMATION FOR SEQ ID NO:38:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 4 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

Gly Gly Gly Ser  
1

## (2) INFORMATION FOR SEQ ID NO:39:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 8 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

Gly Gly Gly Ser Gly Gly Gly Ser  
1 5

## (2) INFORMATION FOR SEQ ID NO:40:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 12 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser  
1 5 10

## (2) INFORMATION FOR SEQ ID NO:41:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 7 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

Ser Gly Gly Ser Gly Gly Ser

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1

5

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 5 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

Glu Phe Gly Asn Met  
1 5

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 6 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

Glu Phe Gly Gly Asn Met  
1 5

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 9 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

Glu Phe Gly Gly Asn Gly Gly Asn Met  
1 5

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 7 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

Gly Gly Ser Asp Met Ala Gly  
1 5

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 5 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

Ser Gly Gly Asn Gly  
1 5

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## (2) INFORMATION FOR SEQ ID NO:47:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

Ser Gly Gly Asn Gly Ser Gly Gly Asn Gly  
 1                      5                      10

## (2) INFORMATION FOR SEQ ID NO:48:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

Ser Gly Gly Asn Gly Ser Gly Gly Asn Gly Ser Gly Gly Asn Gly  
 1                      5                      10                      15

## (2) INFORMATION FOR SEQ ID NO:49:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

Ser Gly Gly Ser Gly Ser Gly Gly Ser Gly  
 1                      5                      10

## (2) INFORMATION FOR SEQ ID NO:50:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

Ser Gly Gly Ser Gly Ser Gly Gly Ser Gly Ser Gly Gly Ser Gly  
 1                      5                      10                      15

## (2) INFORMATION FOR SEQ ID NO:51:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 6 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

Gly Gly Gly Ser Gly Gly  
 1                      5

## (2) INFORMATION FOR SEQ ID NO:52:

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- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 7 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: None

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

Gly Gly Gly Ser Gly Gly Gly  
 1 5

(2) INFORMATION FOR SEQ ID NO:53:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 10 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: None

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly  
 1 5 10

(2) INFORMATION FOR SEQ ID NO:54:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 13 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: None

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly  
 1 5 10

(2) INFORMATION FOR SEQ ID NO:55:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 15 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: None

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly  
 1 5 10 15

(2) INFORMATION FOR SEQ ID NO:56:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 21 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: None

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser  
 1 5 10 15  
 Gly Gly Gly Ser Gly  
 20

(2) INFORMATION FOR SEQ ID NO:57:

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## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 33 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

CTGACCATGG CNACCCAGGA CTGCTCCTTC CAA

33

## (2) INFORMATION FOR SEQ ID NO:58:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 32 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

ACTGAAGCTT AGGGCTGACA CTGCAGCTCC AG

32

## (2) INFORMATION FOR SEQ ID NO:59:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 32 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

ACTGAAGCTT ACAGGGTTGA GGAGTCGGGC TG

32

## (2) INFORMATION FOR SEQ ID NO:60:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 46 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

GACTGCCATG GCNACYCAGG AYTGYTCYTT YCAACACAGC CCCATC

46

## (2) INFORMATION FOR SEQ ID NO:61:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 46 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

GACTGCCATG GCNACYCAGG AYTGYTCYTT YCAACACAGC CCCATC

46

## (2) INFORMATION FOR SEQ ID NO:62:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 22 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

TGTCCAAACT CATCAATGTA TC

22

## (2) INFORMATION FOR SEQ ID NO:63:

102

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## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 38 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

CATGGCCATG GCCGACGAGG AGCTCTGCGG GGGCCTCT 38

## (2) INFORMATION FOR SEQ ID NO:64:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 36 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

GCTAGAAGCT TACTGCAGGT TGGAGGCCAC GGTGAC 36

## (2) INFORMATION FOR SEQ ID NO:65:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 38 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

CATGGCCATG GCCTCCAAGA TGCAAGGCTT GCTGGAGC 38

## (2) INFORMATION FOR SEQ ID NO:66:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 36 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

GCTAGAAGCT TACCCAGCGA CAGTCTTGAG CCGCTC 36

## (2) INFORMATION FOR SEQ ID NO:67:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 36 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

CATGGCCATG GCCCCCCCCA GCTGTCTTCG CTTCGT 36

## (2) INFORMATION FOR SEQ ID NO:68:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 37 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

GCTAGAAGCT TAGGGCTGAA AGGCACATTT GGTGACA 37

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## (2) INFORMATION FOR SEQ ID NO:69:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 42 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

CCCTGTCTGG CGGCAACGGC ACCCAGGACT GCTCCTTCCA AC

42

## (2) INFORMATION FOR SEQ ID NO:70:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 48 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

GCGGTAACGG CAGTGGAGGT AATGGCACCC AGGACTGCTC CTTCCAAC

48

## (2) INFORMATION FOR SEQ ID NO:71:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 57 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

ACGGCAGTGG TGGCAATGGG AGCGGCGGAA ATGGAACCCA GGACTGCTCC TTCCAAC

57

## (2) INFORMATION FOR SEQ ID NO:72:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 38 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

GTGCCGTTGC CGCCAGACAG GGTGAGGAG TCGGGCTG

38

## (2) INFORMATION FOR SEQ ID NO:73:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 48 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

ATTACCTCCA CTGCCGTTAC CGCCTGACAG GGTGAGGAG TCGGGCTG

48

## (2) INFORMATION FOR SEQ ID NO:74:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 54 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

GCTCCCATTG CCACCACTGC CGTTACCTCC AGACAGGGTT GAGGAGTCGG GCTG

54

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## (2) INFORMATION FOR SEQ ID NO:75:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 60 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

GATGAGGATC CGGTGGCAAT GGGAGCGGCG GAAATGGAAC CCAGGACTGC TCCTTCCACC 60

## (2) INFORMATION FOR SEQ ID NO:76:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 45 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:

GATGACGGAT CCGTTACCTC CAGACAGGGT TGAGGAGTCG GGCTG 45

## (2) INFORMATION FOR SEQ ID NO:77:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 46 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

GATGACGGAT CCGGAGGTAA TGGCACCCAG GACTGCTCCT TCCAAC 46

## (2) INFORMATION FOR SEQ ID NO:78:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:

GACTGCCATG GCCGACGAGG AGCTCTGCG 29

## (2) INFORMATION FOR SEQ ID NO:79:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 28 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:

GACTCAAGCT TACTGCAGGT TGGAGGCC 28

## (2) INFORMATION FOR SEQ ID NO:80:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:

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GACTCGGGAT CCGGAGGTTC TGGCACCCAG GACTGCTCC

39

(2) INFORMATION FOR SEQ ID NO:81:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 41 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:

GACTGGGATC CGGTGGCACT GGGAGCGGCG GATCTGGAAC C

41

(2) INFORMATION FOR SEQ ID NO:82:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:

GACTTGGGAT CCACTACCTC CAGACAGGGT TGAGGAGTC

39

(2) INFORMATION FOR SEQ ID NO:83:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:

ACTGACGGAT CCACCGCCCA GGGTTGAGGA GTCGGGCTG

39

(2) INFORMATION FOR SEQ ID NO:84:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 51 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:

ACTGACGGAT CCACCTCCTG ACCCACCGCC CAGGGTTGAG GAGTCGGGCT G

51

(2) INFORMATION FOR SEQ ID NO:85:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 63 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:

ACTGACGGAT CCACCTCCTG ACCCACCTCC TGACCCACCG CCCAGGGTTG AGGAGTCGGG  
CTG60  
63

(2) INFORMATION FOR SEQ ID NO:86:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 28 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:

ACGTAAAGCT TACAGGGTTG AGGAGTCG

28

(2) INFORMATION FOR SEQ ID NO:87:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 40 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:

GTCAGTGGAT CCGGAGGTAC CCAGGACTGC TCCTTCCAAC

40

(2) INFORMATION FOR SEQ ID NO:88:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 43 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:

GTCAGTGGAT CCGGAGGTGG CACCCAGGAC TGCTCCTTCC AAC

43

(2) INFORMATION FOR SEQ ID NO:89:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 60 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:

GTCAGTGGAT CCGGAGGTGG CTCAGGGGGA GGTAGTGGTA CCCAGGACTG CTCCTTCCAC

60

(2) INFORMATION FOR SEQ ID NO:90:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 57 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:

GTTGCCATGG CNTCNAAYCT GCARGAYGAR GARCTGTGCG GGGGCCTCTG GCGGCTG

57

(2) INFORMATION FOR SEQ ID NO:91:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 57 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:

GTTGCCATGG CNAAYCTGCA RGAYGARGAR CTGTGYGGGG GCCTCTGGCG GCTGGTC

57

(2) INFORMATION FOR SEQ ID NO:92:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 57 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:

GTTGCCATGG CNCTGCARGA YGARGARCTG TGYGGYGGCC TCTGGCGGCT GGTCTTG 57

(2) INFORMATION FOR SEQ ID NO:93:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 57 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:

GTTGCCATGG CNCARGAYGA RGARCTGTGY GGYGGYCTCT GGC GGCTGGT CCTGGCA 57

(2) INFORMATION FOR SEQ ID NO:94:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 57 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:

GTTGCCATGG CNGAYGARGA RCTGTGYGGY GGYCTCTGGC GGCTGGTCCT GGCACAG 57

(2) INFORMATION FOR SEQ ID NO:95:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 57 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:

GTTGCCATGG CNGARGARCT GTGYGGYGGY CTCTGGCGGC TGCTCCTGGC ACAGCGC 57

(2) INFORMATION FOR SEQ ID NO:96:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 57 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:96:

GTTGCCATGG CNGARCTGTG YGGYGGYCTG TGGCGYCTGG TCCTGGCACA GCGCTGG 57

(2) INFORMATION FOR SEQ ID NO:97:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 57 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:97:

GTTGCCATGG CNCTGTGYGG YGGYCTGTGG CGYCTGGTCC TGGCACAGCG CTGGATG 57

(2) INFORMATION FOR SEQ ID NO:98:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:98:

TATGCAAGCT TAGGCCACGG TGACTGGGTA

30

(2) INFORMATION FOR SEQ ID NO:99:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:99:

TATGCAAGCT TAGGAGGCCA CGGTGACTGG

30

(2) INFORMATION FOR SEQ ID NO:100:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:100:

TATGCAAGCT TAGTTGGAGG CCACGGTGAC

30

(2) INFORMATION FOR SEQ ID NO:101:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:101:

TATGCAAGCT TACAGGTTGG AGGCCACGGT

30

(2) INFORMATION FOR SEQ ID NO:102:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:102:

TATGCAAGCT TACTGCAGGT TGGAGGCCAC

30

(2) INFORMATION FOR SEQ ID NO:103:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:103:

TATGCAAGCT TAGTCCTGCA GGTTGGAGGC

30

(2) INFORMATION FOR SEQ ID NO:104:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single

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(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:104:

TATGCAAGCT TACTCGTCCT GCAGGTTGGA

30

(2) INFORMATION FOR SEQ ID NO:105:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:105:

TATGCAAGCT TACTCCTCGT CCTGCAGGTT

30

(2) INFORMATION FOR SEQ ID NO:106:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 405 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:106:

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| GCCACCCAGG | ACTGCTCCTT | CCAACACAGC | CCCATCTCCT | CCGACTTCGC | TGTCAAAATC | 60  |
| CGTGAGCTGT | CTGACTACCT | GCTTCAAGAT | TACCCAGTCA | CCGTGGCCTC | CAACCTGCAG | 120 |
| GACGAGGAGC | TCTGCGGGGC | GCTCTGGCGG | CTGGTCCTGG | CACAGCGCTG | GATGGAGCGG | 180 |
| CTCAAGACTG | TCGCTGGGTC | CAAGATGCAA | GGCTTGCTGG | AGCGCGTGAA | CACGGAGATA | 240 |
| CACTTTGTCA | CCAAATGTGC | CTTTCAGCCC | CCCCCAGCT  | GTCTTCGCTT | CGTCCAGACC | 300 |
| AACATCTCCC | GCCTCCTGCA | GGAGACCTCC | GAGCAGCTGG | TGGCGCTGAA | GCCCTGGATC | 360 |
| ACTCGCCAGA | ACTTCTCCCG | GTGCCTGGAG | CTGCAGTGTC | AGCCC      |            | 405 |

(2) INFORMATION FOR SEQ ID NO:107:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 420 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:107:

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| GCCACCCAGG | ACTGCTCCTT | CCAACACAGC | CCCATCTCCT | CCGACTTCGC | TGTCAAAATC | 60  |
| CGTGAGCTGT | CTGACTACCT | GCTTCAAGAT | TACCCAGTCA | CCGTGGCCTC | CAACCTGCAG | 120 |
| GACGAGGAGC | TCTGCGGGGC | CCTCTGGCGG | CTGGTCCTGG | CACAGCGCTG | GATGGAGCGG | 180 |
| CTCAAGACTG | TCGCTGGGTC | CAAGATGCAA | GGCTTGCTGG | AGCGCGTGAA | CACGGAGATA | 240 |
| CACTTTGTCA | CCAAATGTGC | CTTTCAGCCC | CCCCCAGCT  | GTCTTCGCTT | CGTCCAGACC | 300 |
| AACATCTCCC | GCCTCCTGCA | GGAGACCTCC | GAGCAGCTGG | TGGCGCTGAA | GCCCTGGATC | 360 |
| ACTCGCCAGA | ACTTCTCCCG | GTGCCTGGAG | CTGCAGTGTC | AGCCCGACTC | CTCAACCCTG | 420 |

(2) INFORMATION FOR SEQ ID NO:108:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 366 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:108:

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| GCCACCCAGG | ACTGCTCCTT | CCAACACAGC | CCCATCTCCT | CCGACTTCGC | TGTCAAAATC | 60  |
| CGTGAGCTGT | CTGACTACCT | GCTTCAAGAT | TACCCAGTCA | CCGTGGCCTC | CAACCTGCAG | 120 |
| GACGAGGAGC | TCTGCGGGGC | CCTCTGGCGG | CTGGTCCTGG | CACAGCGCTG | GATGGAGCGG | 180 |
| CTCAAGACTG | TCGCTGGGTC | CAAGATGCAA | GGCTTGCTGG | AGCGCGTGAA | CACGGAGATA | 240 |
| CACTTTGTCA | CCAAATGTGC | CTTTCAGGAG | ACCTCCGAGC | AGCTGGTGGC | GCTGAAGCCC | 300 |
| TGGATCACTC | GCCAGAACTT | CTCCCGGTGC | CTGGAGCTGC | AGTGTCAGCC | CGACTCCTCA | 360 |
| ACCCTG     |            |            |            |            |            | 366 |

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## (2) INFORMATION FOR SEQ ID NO:109:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 405 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:109:

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| GGAAGTCAGG | ATTGTTCTTT | CCAACACAGC | CCCATCTCCT | CCGACTTCGC | TGTCAAAATC | 60  |
| CGTGAGCTGT | CTGACTACCT | GCTTCAAGAT | TACCCAGTCA | CCGTGGCCTC | CAACCTGCAG | 120 |
| GACGAGGAGC | TCTGCGGGGG | CCTCTGGCGG | CTGGTCCTGG | CACAGCGCTG | GATGGAGCGG | 180 |
| CTCAAGACTG | TCGCTGGGTC | CAAGATGCAA | GGCTTGCTGG | AGCGCGTGAA | CACGGAGATA | 240 |
| CACTTTGTCA | CCAAATGTGC | CTTTCAGCCC | CCCCCAGCT  | GTCTTCGCTT | CGTCCAGACC | 300 |
| AACATCTCCC | GCCTCCTGCA | GGAGACCTCC | GAGCAGCTGG | TGGCGCTGAA | GCCCTGGATC | 360 |
| ACTCGCCAGA | ACTTCTCCCG | GTGCCTGGAG | CTGCAGTGTC | AGCCC      |            | 405 |

## (2) INFORMATION FOR SEQ ID NO:110:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 420 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:110:

|            |            |            |            |            |             |     |
|------------|------------|------------|------------|------------|-------------|-----|
| GGTACCCAGG | ATTGTTCTTT | CCAACACAGC | CCCATCTCCT | CCGACTTCGC | TGTCAAAATC  | 60  |
| CGTGAGCTGT | CTGACTACCT | GCTTCAAGAT | TACCCAGTCA | CCGTGGCCTC | CAACCTGCAG  | 120 |
| GACGAGGAGC | TCTGCGGGGG | CCTCTGGCGG | CTGGTCCTGG | CACAGCGCTG | GATGGAGCGG  | 180 |
| CTCAAGACTG | TCGCTGGGTC | CAAGATGCAA | GGCTTGCTGG | AGCGCGTGAA | CACGGAGATA  | 240 |
| CACTTTGTCA | CCAAATGTGC | CTTTCAGCCC | CCCCCAGCT  | GTCTTCGCTT | CGTCCAGACC  | 300 |
| AACATCTCCC | GCCTCCTGCA | GGAGACCTCC | GAGCAGCTGG | TGGCGCTGAA | GCCCTGGATC  | 360 |
| ACTCGCCAGA | ACTTCTCCCG | GTGCCTGGAG | CTGCAGTGTC | AGCCCGACTC | CTCAACCCCTG | 420 |

## (2) INFORMATION FOR SEQ ID NO:111:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 405 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:111:

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| GCCACTCAGG | ACTGTTCTTT | CCAACACAGC | CCCATCTCCT | CCGACTTCGC | TGTCAAAATC | 60  |
| CGTGAGCTGT | CTGACTACCT | GCTTCAAGAT | TACCCAGTCA | CCGTGGCCTC | CAACCTGCAG | 120 |
| GACGAGGAGC | TCTGCGGGGG | CCTCTGGCGG | CTGGTCCTGG | CACAGCGCTG | GATGGAGCGG | 180 |
| CTCAAGACTG | TCGCTGGGTC | CAAGATGCAA | GGCTTGCTGG | AGCGCGTGAA | CACGGAGATA | 240 |
| CACTTTGTCA | CCAAATGTGC | CTTTCAGCCC | CCCCCAGCT  | GTCTTCGCTT | CGTCCAGACC | 300 |
| AACATCTCCC | GCCTCCTGCA | GGAGACCTCC | GAGCAGCTGG | TGGCGCTGAA | GCCCTGGATC | 360 |
| ACTCGCCAGA | ACTTCTCCCG | GTGCCTGGAG | CTGCAGTGTC | AGCCC      |            | 405 |

## (2) INFORMATION FOR SEQ ID NO:112:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 420 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:112:

|            |            |            |            |            |             |     |
|------------|------------|------------|------------|------------|-------------|-----|
| GCCACTCAGG | ACTGCTCTTT | TCAACACAGC | CCCATCTCCT | CCGACTTCGC | TGTCAAAATC  | 60  |
| CGTGAGCTGT | CTGACTACCT | GCTTCAAGAT | TACCCAGTCA | CCGTGGCCTC | CAACCTGCAG  | 120 |
| GACGAGGAGC | TCTGCGGGGG | CCTCTGGCGG | CTGGTCCTGG | CACAGCGCTG | GATGGAGCGG  | 180 |
| CTCAAGACTG | TCGCTGGGTC | CAAGATGCAA | GGCTTGCTGG | AGCGCGTGAA | CACGGAGATA  | 240 |
| CACTTTGTCA | CCAAATGTGC | CTTTCAGCCC | CCCCCAGCT  | GTCTTCGCTT | CGTCCAGACC  | 300 |
| AACATCTCCC | GCCTCCTGCA | GGAGACCTCC | GAGCAGCTGG | TGGCGCTGAA | GCCCTGGATC  | 360 |
| ACTCGCCAGA | ACTTCTCCCG | GTGCCTGGAG | CTGCAGTGTC | AGCCCGACTC | CTCAACCCCTG | 420 |

## (2) INFORMATION FOR SEQ ID NO:113:

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- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 465 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:113:

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| GCCGACGAGG | AGCTCTGCGG | GGGCCTCTGG | CGGCTGGTCC | TGGCACAGCG | CTGGATGGAG | 60  |
| CGGCTCAAGA | CTGTCGCTGG | GTCCAAGATG | CAAGGCTTGC | TGGAGCGCGT | GAACACGGAG | 120 |
| ATACACTTTG | TCACCAAATG | TGCCTTTCAG | CCCCCCCCCA | GCTGTCTTCG | CTTCGTCCAG | 180 |
| ACCAACATCT | CCCGCCTCCT | GCAGGAGACC | TCCGAGCAGC | TGGTGGCGCT | GAAGCCCTGG | 240 |
| ATCACTCGCC | AGAACTTCTC | CCGGTGCCTG | GAGCTGCAGT | GTCAGCCCGA | CTCCTCAACC | 300 |
| CTGTCTGGAG | GTAACGGATC | CGGTGGCAAT | GGGAGCGGCG | GAAATGGAAC | CCAGGACTGC | 360 |
| TCCTTCCAAC | ACAGCCCCAT | CTCCTCCGAC | TTCGCTGTCA | AAATCCGTGA | GCTGTCTGAC | 420 |
| TACCTGCTTC | AAGATTACCC | AGTCACCGTG | GCCTCCAACC | TGCAG      |            | 465 |

(2) INFORMATION FOR SEQ ID NO:114:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 450 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:114:

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| GCCGACGAGG | AGCTCTGCGG | GGGCCTCTGG | CGGCTGGTCC | TGGCACAGCG | CTGGATGGAG | 60  |
| CGGCTCAAGA | CTGTCGCTGG | GTCCAAGATG | CAAGGCTTGC | TGGAGCGCGT | GAACACGGAG | 120 |
| ATACACTTTG | TCACCAAATG | TGCCTTTCAG | CCCCCCCCCA | GCTGTCTTCG | CTTCGTCCAG | 180 |
| ACCAACATCT | CCCGCCTCCT | GCAGGAGACC | TCCGAGCAGC | TGGTGGCGCT | GAAGCCCTGG | 240 |
| ATCACTCGCC | AGAACTTCTC | CCGGTGCCTG | GAGCTGCAGT | GTCAGCCCGA | CTCCTCAACC | 300 |
| CTGTCAAGCG | GTAACGGCAG | TGGAGGTAAT | GGCACCCAGG | ACTGCTCCTT | CCAACACAGC | 360 |
| CCCATCTCCT | CCGACTTCGC | TGTCAAAATC | CGTGAGCTGT | CTGACTACCT | GCTTCAAGAT | 420 |
| TACCCAGTCA | CCGTGGCCTC | CAACCTGCAG |            |            |            | 450 |

(2) INFORMATION FOR SEQ ID NO:115:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 435 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:115:

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| GCCGACGAGG | AGCTCTGCGG | GGGCCTCTGG | CGGCTGGTCC | TGGCACAGCG | CTGGATGGAG | 60  |
| CGGCTCAAGA | CTGTCGCTGG | GTCCAAGATG | CAAGGCTTGC | TGGAGCGCGT | GAACACGGAG | 120 |
| ATACACTTTG | TCACCAAATG | TGCCTTTCAG | CCCCCCCCCA | GCTGTCTTCG | CTTCGTCCAG | 180 |
| ACCAACATCT | CCCGCCTCCT | GCAGGAGACC | TCCGAGCAGC | TGGTGGCGCT | GAAGCCCTGG | 240 |
| ATCACTCGCC | AGAACTTCTC | CCGGTGCCTG | GAGCTGCAGT | GTCAGCCCGA | CTCCTCAACC | 300 |
| CTGTCTGGCG | GCAACGGCAC | CCAGGACTGC | TCCTTCCAAC | ACAGCCCCAT | CTCCTCCGAC | 360 |
| TTCGCTGTCA | AAATCCGTGA | GCTGTCTGAC | TACCTGCTTC | AAGATTACCC | AGTCACCGTG | 420 |
| GCCTCCAACC | TGCAG      |            |            |            |            | 435 |

(2) INFORMATION FOR SEQ ID NO:116:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 465 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:116:

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| GCCTCCAAGA | TGCAAGGCTT | GCTGGAGCGC | GTGAACACGG | AGATACACTT | TGTACCAAAA | 60  |
| TGTGCCTTTC | AGCCCCCCCC | CAGCTGTCTT | CGCTTCGTCC | AGACCAACAT | CTCCCGCCTC | 120 |
| CTGCAGGAGA | CCTCCGAGCA | GCTGGTGGCG | CTGAAGCCCT | GGATCACTCG | CCAGAAGTTC | 180 |
| TCCCGGTGCC | TGGAGCTGCA | GTGTCAGCCC | GACTCCTCAA | CCCTGTCTGG | AGGTAACGGA | 240 |
| TCCGGTGGCA | ATGGGAGCGG | CGGAAATGGA | ACCCAGGACT | GCTCCTTCCA | ACACAGCCCC | 300 |
| ATCTCCTCCG | ACTTCGCTGT | CAAAATCCGT | GAGCTGTCTG | ACTACCTGCT | TCAAGATTAC | 360 |
| CCAGTCACCG | TGGCCTCCAA | CCTGCAGGAC | GAGGAGCTCT | GCGGGGGCCT | CTGGCGGCTG | 420 |

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GTCCTGGCAC AGCGCTGGAT GGAGCGGCTC AAGACTGTCTG CTGGG

465

## (2) INFORMATION FOR SEQ ID NO:117:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 450 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:117:

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| GCCTCCAAGA | TGCAAGGCTT | GCTGGAGCGC | GTGAACACGG | AGATACACTT | TGTCACCAAA | 60  |
| TGTGCCTTTC | AGCCCCCCCC | CAGCTGTCTT | CGCTTCGTCC | AGACCAACAT | CTCCCGCCTC | 120 |
| CTGCAGGAGA | CCTCCGAGCA | GCTGGTGGCG | CTGAAGCCCT | GGATCACTCG | CCAGAACTTC | 180 |
| TCCCGGTGCC | TGGAGCTGCA | GTGTCAGCCC | GACTCCTCAA | CCCTGTCTGG | AGGTAACGGA | 240 |
| TCCGGAGGTA | ATGGCACCCA | GGACTGTCTC | TTCCAACACA | GCCCCATCTC | CTCCGACTTC | 300 |
| GCTGTCAAAA | TCCGTGAGCT | GTCTGACTAC | CTGCTTCAAG | ATTACCCAGT | CACCGTGGCC | 360 |
| TCCAACCTGC | AGGACGAGGA | GCTCTGCGGG | GGCCTCTGGC | GGCTGGTCCT | GGCACAGCGC | 420 |
| TGGATGAGAG | GGCTCAAGAC | TGTCGCTGGG |            |            |            | 450 |

## (2) INFORMATION FOR SEQ ID NO:118:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 435 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:118:

|             |            |            |            |            |            |     |
|-------------|------------|------------|------------|------------|------------|-----|
| GCCTCCAAGA  | TGCAAGGCTT | GCTGGAGCGC | GTGAACACGG | AGATACACTT | TGTCACCAAA | 60  |
| TGTGCCTTTC  | AGCCCCCCCC | CAGCTGTCTT | CGCTTCGTCC | AGACCAACAT | CTCCCGCCTC | 120 |
| CTGCAGGAGA  | CCTCCGAGCA | GCTGGTGGCG | CTGAAGCCCT | GGATCACTCG | CCAGAACTTC | 180 |
| TCCCGGTGCC  | TGGAGCTGCA | GTGTCAGCCC | GACTCCTCAA | CCCTGTCTGG | CGGCAACGGC | 240 |
| ACGCAGGACT  | GCTCCTTCCA | ACACAGCCCC | ATCTCCTCCG | ACTTCGCTGT | CAAAATCCGT | 300 |
| GAGCTGTCTG  | ACTACCTGCT | TCAAGATTAC | CCAGTCACCG | TGGCCTCCAA | CCTGCAGGAC | 360 |
| GAGGAGCTCT  | GCGGGGGCCT | CTGGCGGCTG | GTCCTGGCAC | AGCGCTGGAT | GGAGCGGCTC | 420 |
| AAGACTGTCTG | CTGGG      |            |            |            |            | 435 |

## (2) INFORMATION FOR SEQ ID NO:119:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 465 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:119:

|            |            |             |            |            |            |     |
|------------|------------|-------------|------------|------------|------------|-----|
| GCCCCCCCCA | GCTGTCTTCG | CTTCGTCCAG  | ACCAACATCT | CCCGCCTCCT | GCAGGAGACC | 60  |
| TCCGAGCAGC | TGGTGGCGCT | GAAGCCCTGG  | ATCACTCGCC | AGAACTTCTC | CCGGTGCCTG | 120 |
| GAGCTGCAGT | GTCAGCCCGA | CTCCTCAACC  | CTGTCTGGAG | GTAACGGCAG | TGGTGGCAAT | 180 |
| GGGAGCGGTG | GAAATGGAAC | CCAGGACTGC  | TCCTTCCAAC | ACAGCCCCAT | CTCCTCCGAC | 240 |
| TTGCTGTGTA | AAATCCGTGA | GCTGTCTGAC  | TACCTGCTTC | AAGATTACCC | AGTCACCGTG | 300 |
| GCCTCCAACC | TGCAGGACGA | GGAGCTCTGC  | GGGGGCTCT  | GGCGGTGGT  | CCTGGCACAG | 360 |
| CGCTGGATGG | AGCGGCTCAA | GACTGTCTGCT | GGGTCCAAGA | TGCAAGGCTT | GCTGGAGCGC | 420 |
| GTGAACACGG | AGATACACTT | TGTCACCAAA  | TGTGCCTTTC | AGCCC      |            | 465 |

## (2) INFORMATION FOR SEQ ID NO:120:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 450 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:120:

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| GCCCCCCCCA | GCTGTCTTCG | CTTCGTCCAG | ACCAACATCT | CCCGCCTCCT | GCAGGAGACC | 60  |
| TCCGAGCAGC | TGGTGGCGCT | GAAGCCCTGG | ATCACTCGCC | AGAACTTCTC | CCGGTGCCTG | 120 |
| GAGCTGCAGT | GTCAGCCCGA | CTCCTCAACC | CTGTCTGGAG | GTAACGGCAG | TGGAGGTAAT | 180 |
| GGCACCCAGG | ACTGCTCCTT | CCAACACAGC | CCCATCTCCT | CCGACTTCGC | TGTCAAAATC | 240 |

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|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| CGTGAGCTGT | CTGACTACCT | GCTTCAAGAT | TACCCAGTCA | CCGTGGCCTC | CAACCTGCAG | 300 |
| GACGAGGAGC | TCTGCGGGGG | CCTCTGGCGG | CTGGTCCTGG | CACAGCGCTG | GATGGAGCGG | 360 |
| CTCAAGACTG | TCGCTGGGTC | CAAGATGCAA | GGCTTGCTGG | AGCGCGTGAA | CACGGAGATA | 420 |
| CACTTTGTC  | CCAAATGTGC | CTTTCAGCCC |            |            |            | 450 |

## (2) INFORMATION FOR SEQ ID NO:121:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 435 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:121:

|            |            |            |            |            |             |     |
|------------|------------|------------|------------|------------|-------------|-----|
| GCCCCCCCCA | GCTGTCTTCG | CTTCGTCCAG | ACCAACATCT | CCCGCCTCCT | GCAGGAGACC  | 60  |
| TCCGAGCAGC | TGGTGGCGCT | GAAGCCCTGG | ATCACTCGCC | AGAACTTCTC | CCGGTGCCTG  | 120 |
| GAGCTGCAGT | GTCAGCCCGA | CTCCTCAACC | CTGTCTGGCG | GCAACGGCAC | GCAGGACTGC  | 180 |
| TCCTTCCAAC | ACAGCCCCAT | CTCCTCCGAC | TTGCTGTCTA | AAATCCGTGA | GCTGTCTGAC  | 240 |
| TACCTGCTTC | AAGATTACCC | AGTCACCGTG | GCCTCCAACC | TGCAGGACGA | GGAGCTCTGC  | 300 |
| GGGGGCCTCT | GGCGGCTGGT | CCTGGCACAG | CGCTGGATGG | AGCGGCTCAA | GACTGTCTGCT | 360 |
| GGGTCCAAGA | TGCAAGGCTT | GCTGGAGCGC | GTGAACACGG | AGATACTACT | TGTCACCAAA  | 420 |
| TGTGCCTTTC | AGCCC      |            |            |            |             | 435 |

## (2) INFORMATION FOR SEQ ID NO:122:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 451 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:122:

|            |             |            |            |            |            |     |
|------------|-------------|------------|------------|------------|------------|-----|
| GCCGACGAGG | AGCTCTGCGG  | GGGCCTCTGG | CGGCTGGTCC | TGGCACAGCG | CTGGATGGAG | 60  |
| CGGCTCAAGA | CTGTGCTGG   | GTCCAAGATG | CAAGGCTTGC | TGGAGCGCGT | GAACACGGAG | 120 |
| ATACACTTTG | TCACCAAATG  | TGCCTTTCAG | CCCCCCCCCA | GCTGTCTTCG | CTTCGTCCAG | 180 |
| ACCAACATCT | CCCGCCTCCT  | GCAGGAGACC | TCCGAGCAGC | TGGTGGCGCT | GAAGCCCTGG | 240 |
| ATCACTCGCC | AGAACTTCTC  | CCGGTGCCTG | GAGCTGCAGT | GTCAGCCCGA | CTCCTCAACC | 300 |
| CTGTCTGGAG | GTAAGTGGATC | CGGAGGTTCT | GGCAACCCAG | GACTGTCTCT | TCCAACACAG | 360 |
| CCCCATCTCC | TCCGACTTCG  | CTGTCAAAAT | CCGTGAGCTG | TCTGACTACC | TGCTTCAAGA | 420 |
| TTACCCAGTC | ACCGTGGCCT  | CCAACCTGCA | G          |            |            | 451 |

## (2) INFORMATION FOR SEQ ID NO:123:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 465 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:123:

|            |             |            |            |            |            |     |
|------------|-------------|------------|------------|------------|------------|-----|
| GCCGACGAGG | AGCTCTGCGG  | GGGCCTCTGG | CGGCTGGTCC | TGGCACAGCG | CTGGATGGAG | 60  |
| CGGCTCAAGA | CTGTGCTGG   | GTCCAAGATG | CAAGGCTTGC | TGGAGCGCGT | GAACACGGAG | 120 |
| ATACACTTTG | TCACCAAATG  | TGCCTTTCAG | CCCCCCCCCA | GCTGTCTTCG | CTTCGTCCAG | 180 |
| ACCAACATCT | CCCGCCTCCT  | GCAGGAGACC | TCCGAGCAGC | TGGTGGCGCT | GAAGCCCTGG | 240 |
| ATCACTCGCC | AGAACTTCTC  | CCGGTGCCTG | GAGCTGCAGT | GTCAGCCCGA | CTCCTCAACC | 300 |
| CTGTCTGGAG | GTAAGTGGATC | CGGTGGCAGT | GGGAGCGGCG | GATCTGGAAC | CCAGGACTGC | 360 |
| TCCTTCCAAC | ACAGCCCCAT  | CTCCTCCGAC | TTGCTGTCTA | AAATCCGTGA | GCTGTCTGAC | 420 |
| TACCTGCTTC | AAGATTACCC  | AGTCACCGTG | GCCTCCAACC | TGCAG      |            | 465 |

## (2) INFORMATION FOR SEQ ID NO:124:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 437 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:124:

|            |            |            |            |            |            |    |
|------------|------------|------------|------------|------------|------------|----|
| CCATGGCCAC | CCAGGACTGC | TCCTTCCAAC | ACAGCCCCAT | CTCCTCCGAC | TTGCTGTCTA | 60 |
|------------|------------|------------|------------|------------|------------|----|

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|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| AAATCCGTGA | GCTGTCTGAC | TACCTGCTTC | AAGATTACCC | AGTCACCGTG | GCCTCCAACC | 120 |
| TGCAGGACGA | GGAGCTCTGC | GGGGGCCTCT | GGCGGCTGGT | CCTGGCACAG | CGCTGGATGG | 180 |
| AGCGGCTCAA | GACTGTGCGT | GGGTCCAAGA | TGCAAGGCTT | GCTGGAGCGC | GTGAACACGG | 240 |
| AGATACACTT | TGTCACCAAA | TGTGCCTTTC | AGCCCCCCCC | CAGCTGTCTT | CGCTTCGTCC | 300 |
| AGACCAACAT | CTCCCGCCTC | CTGCAGGAGA | CCTCCGAGCA | GCTGGTGGCG | CTGAAGCCCT | 360 |
| GGATCACTCG | CCAGAACTTC | TCCCGGTGCC | TGGAGCTGCA | GTGTCAGCCC | GACTCCTCAA | 420 |
| CCCTGGGCGG | TGGATCC    |            |            |            |            | 437 |

## (2) INFORMATION FOR SEQ ID NO:125:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 436 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:125:

|            |            |            |            |            |             |     |
|------------|------------|------------|------------|------------|-------------|-----|
| GGATCCGGAG | GTACCCAGGA | CTGCTCCTTC | CAACACAGCC | CCATCTCCTC | CGACTTCGCT  | 60  |
| GTCAAAATCC | GTGAGCTGTC | TGACTACCTG | CTTCAAGATT | ACCCAGTCAC | CGTGGCCTCC  | 120 |
| AACCTGCAGG | ACGAGGAGCT | CTGCGGGGGC | CTCTGGCGGC | TGGTCCTGGC | ACAGCGCTGG  | 180 |
| ATGGAGCGGC | TCAAGACTGT | CGCTGGGTCC | AAGATGCAAG | GCTTGCTGGA | GCGCGTGAAC  | 240 |
| ACGGAGATAC | ACTTTGTCAC | CAAATGTGCC | TTTCAGCCCC | CCCCCAGCTG | TCTTCGCTTC  | 300 |
| GTCAGACCA  | ACATCTCCCG | CCTCCTGCAG | GAGACCTCCG | AGCAGCTGGT | GGCGCTGAAG  | 360 |
| CCCTGGATCA | CTCGCCAGAA | CTTCTCCCGG | TGCCTGGAGC | TGCAGTGTC  | GCCCCGACTCC | 420 |
| TCAACCTGT  | AAGCTT     |            |            |            |             | 436 |

## (2) INFORMATION FOR SEQ ID NO:126:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 449 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:126:

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| CCATGGCCAC | CCAGGACTGC | TCCTTCCAAC | ACAGCCCCAT | CTCCTCCGAC | TTGCTGTCA  | 60  |
| AAATCCGTGA | GCTGTCTGAC | TACCTGCTTC | AAGATTACCC | AGTCACCGTG | GCCTCCAACC | 120 |
| TGCAGGACGA | GGAGCTCTGC | GGGGGCCTCT | GGCGGCTGGT | CCTGGCACAG | CGCTGGATGG | 180 |
| AGCGGCTCAA | GACTGTGCGT | GGGTCCAAGA | TGCAAGGCTT | GCTGGAGCGC | GTGAACACGG | 240 |
| AGATACACTT | TGTCACCAAA | TGTGCCTTTC | AGCCCCCCCC | CAGCTGTCTT | CGCTTCGTCC | 300 |
| AGACCAACAT | CTCCCGCCTC | CTGCAGGAGA | CCTCCGAGCA | GCTGGTGGCG | CTGAAGCCCT | 360 |
| GGATCACTCG | CCAGAACTTC | TCCCGGTGCC | TGGAGCTGCA | GTGTCAGCCC | GACTCCTCAA | 420 |
| CCCTGGGCGG | TGGGTCAGGA | GGTGGATCC  |            |            |            | 449 |

## (2) INFORMATION FOR SEQ ID NO:127:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 439 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:127:

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| GGATCCGGAG | GTGGCACCCA | GGACTGCTCC | TTCCAACACA | GCCCCATCTC | CTCCGACTTC | 60  |
| GCTGTCAAAA | TCCGTGAGCT | GTCTGACTAC | CTGCTTCAAG | ATTACCCAGT | CACCGTGGCC | 120 |
| TCCAACCTGC | AGGACGAGGA | GCTCTGCGGG | GGCCTCTGGC | GGCTGGTCCT | GGCACAGCGC | 180 |
| TGGATGGAGC | GGCTCAAGAC | TGTCGCTGGG | TCCAAGATGC | AAGGCTTGCT | GGAGCGCGTG | 240 |
| AACACGGAGA | TACACTTTGT | CACCAAATGT | GCCTTTCAGC | CCCCCCCCAG | CTGTCTTCGC | 300 |
| TTCGTCCAGA | CCAACATCTC | CCGCCTCCTG | CAGGAGACCT | CCGAGCAGCT | GGTGGCGCTG | 360 |
| AAGCCCTGGA | TCACTCGCCA | GAACCTCTCC | CGGTGCCTGG | AGCTGCAGTG | TCAGCCCGAC | 420 |
| TCCTCAACCC | TGTAAGCTT  |            |            |            |            | 439 |

## (2) INFORMATION FOR SEQ ID NO:128:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 461 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

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## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:128:

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| CCATGGCCAC | CCAGGACTGC | TCCTTCCAAC | ACAGCCCCAT | CTCCTCCGAC | TTGCTGTCA  | 60  |
| AAATCCGTGA | GCTGTCTGAC | TACCTGCTTC | AAGATTACCC | AGTCACCGTG | GCCTCCAACC | 120 |
| TGCAGGACGA | GGAGCTCTGC | GGGGGCCTCT | GGCGGCTGGT | CCTGGCACAG | CGCTGGATGG | 180 |
| AGCGGCTCAA | GACTGTGCT  | GGGTCCAAGA | TGCAAGGCTT | GCTGGAGCGC | GTGAACACGG | 240 |
| AGATACACTT | TGTACCAAAA | TGTGCCTTTC | AGCCCCCCCC | CAGCTGTCTT | CGCTTCGTCC | 300 |
| AGACCAACAT | CTCCCGCCTC | CTGCAGGAGA | CCTCCGAGCA | GCTGGTGGCG | CTGAAGCCCT | 360 |
| GGATCACTCG | CCAGAACTTC | TCCCGGTGCC | TGGAGCTGCA | GTGTCAGCCC | GACTCCTCAA | 420 |
| CCCTGGGCGG | TGGGTCAGGA | GGTGGGTCAG | GAGGTGGATC | C          |            | 461 |

## (2) INFORMATION FOR SEQ ID NO:129:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 457 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:129:

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| GGATCCGGAG | GTGGCTCAGG | GGGAGGTAGT | GGTACCCAGG | ACTGCTCCTT | CCAACACAGC | 60  |
| CCCATCTCCT | CCGACTTCGC | TGTCAAAATC | CGTGAGCTGT | CTGACTACCT | GCTTCAAGAT | 120 |
| TACCCAGTCA | CCGTGGCCTC | CAACCTGCGC | GACGAGGAGC | TCTGCGGGGG | CCTCTGGCGG | 180 |
| CTGGTCTCTG | CACAGCGCTG | GATGGAGCGG | CTCAAGACTG | TCGCTGGGTC | CAAGATGCAA | 240 |
| GGCTTGCTGG | AGCGCGTGAA | CACGGAGATA | CACTTTGTCA | CCAAATGTGC | CTTTCAGCCC | 300 |
| CCCCCAGCT  | GTCTTCGCTT | CGTCCAGACC | AACATCTCCC | GCCTCCTGCA | GGAGACCTCC | 360 |
| GAGCAGCTGG | TGGCGCTGAA | GCCCTGGATC | ACTCGCCAGA | ACTTCTCCCG | GTGCCTGGAG | 420 |
| CTGCAGTGTC | AGCCCGACTC | CTCAACCTTG | TAAGCTT    |            |            | 457 |

## (2) INFORMATION FOR SEQ ID NO:130:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 438 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:130:

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| GCCGACGAGG | AGCTCTGCGG | GGGCCTCTGG | CGGCTGGTCC | TGGCACAGCG | CTGGATGGAG | 60  |
| CGGCTCAAGA | CTGTGCTGG  | GTCCAAGATG | CAAGGCTTGC | TGGAGCGCGT | GAACACGGAG | 120 |
| ATACACTTTG | TCACCAAATG | TGCCTTTCAG | CCCCCCCCCA | GCTGTCTTCG | CTTCGTCCAG | 180 |
| ACCAACATCT | CCCGCCTCCT | GCAGGAGACC | TCCGAGCAGC | TGGTGGCGCT | GAAGCCCTGG | 240 |
| ATCACTCGCC | AGAACTTCTC | CCGGTGCCTG | GAGCTGCAGT | GTCAGCCCGA | CTCCTCAACC | 300 |
| CTGGGCGGTG | GATCCGGAGG | TACCCAGGAC | TGCTCCTTCC | AACACAGCCC | CATCTCCTCC | 360 |
| GACTTCGCTG | TCAAATCCG  | TGAGCTGTCT | GACTACCTGC | TTCAAGATTA | CCAGTCACC  | 420 |
| GTGGCCTCCA | ACCTGCAG   |            |            |            |            | 438 |

## (2) INFORMATION FOR SEQ ID NO:131:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 441 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:131:

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| GCCGACGAGG | AGCTCTGCGG | GGGCCTCTGG | CGGCTGGTCC | TGGCACAGCG | CTGGATGGAG | 60  |
| CGGCTCAAGA | CTGTGCTGG  | GTCCAAGATG | CAAGGCTTGC | TGGAGCGCGT | GAACACGGAG | 120 |
| ATACACTTTG | TCACCAAATG | TGCCTTTCAG | CCCCCCCCCA | GCTGTCTTCG | CTTCGTCCAG | 180 |
| ACCAACATCT | CCCGCCTCCT | GCAGGAGACC | TCCGAGCAGC | TGGTGGCGCT | GAAGCCCTGG | 240 |
| ATCACTCGCC | AGAACTTCTC | CCGGTGCCTG | GAGCTGCAGT | GTCAGCCCGA | CTCCTCAACC | 300 |
| CTGGGCGGTG | GATCCGGAGG | TGGCACCCAG | GACTGCTCCT | TCCAACACAG | CCCCATCTCC | 360 |
| TCCGACTTCG | CTGTCAAAAT | CCGTGAGCTG | TCTGACTACC | TGCTTCAAGA | TTACCCAGTC | 420 |
| ACCGTGGCCT | CCAACCTGCA | G          |            |            |            | 441 |

## (2) INFORMATION FOR SEQ ID NO:132:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 450 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single

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(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:132:

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| GCCGACGAGG | AGCTCTGCGG | GGGCCTCTGG | CGGCTGGTCC | TGGCACAGCG | CTGGATGGAG | 60  |
| CGGCTCAAGA | CTGTGCGTGG | GTCCAAGATG | CAAGGCTTGC | TGGAGCGCGT | GAACACGGAG | 120 |
| ATACACTTTG | TCACCAAATG | TGCCTTTCAG | CCCCCCCCCA | GCTGTCTTCG | CTTCGTCCAG | 180 |
| ACCAACATCT | CCCGCCTCCT | GCAGGAGACC | TCCGAGCAGC | TGGTGGCGCT | GAAGCCCTGG | 240 |
| ATCACTCGCC | AGAACTTCTC | CCGGTGCCTG | GAGCTGCAGT | GTCAGCCCGA | CTCCTCAACC | 300 |
| CTGGGCGGTG | GGTCAGGAGG | TGGATCCGGA | GGTACCCAGG | ACTGCTCCTT | CCAACACAGC | 360 |
| CCCATCTCCT | CCGACTTCGC | TGTCAAAATC | CGTGAGCTGT | CTGACTACCT | GCTTCAAGAT | 420 |
| TACCCAGTCA | CCGTGGCCTC | CAACCTGCAG |            |            |            | 450 |

(2) INFORMATION FOR SEQ ID NO:133:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 459 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:133:

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| GCCGACGAGG | AGCTCTGCGG | GGGCCTCTGG | CGGCTGGTCC | TGGCACAGCG | CTGGATGGAG | 60  |
| CGGCTCAAGA | CTGTGCGTGG | GTCCAAGATG | CAAGGCTTGC | TGGAGCGCGT | GAACACGGAG | 120 |
| ATACACTTTG | TCACCAAATG | TGCCTTTCAG | CCCCCCCCCA | GCTGTCTTCG | CTTCGTCCAG | 180 |
| ACCAACATCT | CCCGCCTCCT | GCAGGAGACC | TCCGAGCAGC | TGGTGGCGCT | GAAGCCCTGG | 240 |
| ATCACTCGCC | AGAACTTCTC | CCGGTGCCTG | GAGCTGCAGT | GTCAGCCCGA | CTCCTCAACC | 300 |
| CTGGGCGGTG | GATCCGGAGG | TGGTTCAGGG | GGAGGTAGTG | GTACCCAGGA | CTGCTCCTTC | 360 |
| CAACACAGCC | CCATCTCCTC | CGACTTCGCT | GTCAAAATCC | GTGAGCTGTC | TGACTACCTG | 420 |
| CTTCAAGATT | ACCCAGTCAC | CGTGGCCTCC | AACCTGCAG  |            |            | 459 |

(2) INFORMATION FOR SEQ ID NO:134:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 465 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:134:

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| GCCGACGAGG | AGCTCTGCGG | GGGCCTCTGG | CGGCTGGTCC | TGGCACAGCG | CTGGATGGAG | 60  |
| CGGCTCAAGA | CTGTGCGTGG | GTCCAAGATG | CAAGGCTTGC | TGGAGCGCGT | GAACACGGAG | 120 |
| ATACACTTTG | TCACCAAATG | TGCCTTTCAG | CCCCCCCCCA | GCTGTCTTCG | CTTCGTCCAG | 180 |
| ACCAACATCT | CCCGCCTCCT | GCAGGAGACC | TCCGAGCAGC | TGGTGGCGCT | GAAGCCCTGG | 240 |
| ATCACTCGCC | AGAACTTCTC | CCGGTGCCTG | GAGCTGCAGT | GTCAGCCCGA | CTCCTCAACC | 300 |
| CTGGGCGGTG | GGTCAGGAGG | TGGGTCAGGA | GGTGGATCCG | GAGGTGGCAC | CCAGGACTGC | 360 |
| TCCTTCCAAC | ACAGCCCCAT | CTCCTCCGAC | TTCGCTGTCA | AAATCCGTGA | GCTGTCTGAC | 420 |
| TACCTGCTTC | AAGATTACCC | AGTCACCGTG | GCCTCCAACC | TGCAG      |            | 465 |

(2) INFORMATION FOR SEQ ID NO:135:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 483 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:135:

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| GCCGACGAGG | AGCTCTGCGG | GGGCCTCTGG | CGGCTGGTCC | TGGCACAGCG | CTGGATGGAG | 60  |
| CGGCTCAAGA | CTGTGCGTGG | GTCCAAGATG | CAAGGCTTGC | TGGAGCGCGT | GAACACGGAG | 120 |
| ATACACTTTG | TCACCAAATG | TGCCTTTCAG | CCCCCCCCCA | GCTGCTTTCG | CTTCGTCCAG | 180 |
| ACCAACATCT | CCCGCCTCCT | GCAGGAGACC | TCCGAGCAGC | TGGTGGCGCT | GAAGCCCTGG | 240 |
| ATCACTCGCC | AGAACTTCTC | CCGGTGCCTG | GAGCTGCAGT | GTCAGCCCGA | CTCCTCAACC | 300 |
| CTGGGCGGTG | GGTCAGGAGG | TGGGTCAGGA | GGTGGATCCG | GAGGTGGCTC | AGGGGGAGGT | 360 |
| AGTGGTACCC | AGGACTGCTC | CTTCCAACAC | AGCCCCATCT | CCTCCGACTT | CGCTGTCAAA | 420 |
| ATCCGTGAGC | TGCTGACTA  | CCTGCTTCAA | GATTACCCAG | TCACCGTGCC | CTCCAACCTG | 480 |
| CAG        |            |            |            |            |            | 483 |

(2) INFORMATION FOR SEQ ID NO:136:

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## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 465 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:136:

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| GCCGATTACC | CAGTCACCGT | GGCCTCCAAC | CTGCAGGACG | AGGAGCTCTG | CGGGGGCCTC | 60  |
| TGGCGGCTGG | TCCTGGCACA | GCGCTGGATG | GAGCGGCTCA | AGACTGTGCG | TGGGTCCAAG | 120 |
| ATGCAAGGCT | TGCTGGAGCG | CGTGAACACG | GAGATACACT | TTGTCACCAA | ATGTGCCTTT | 180 |
| CAGCCCCCCC | CCAGCTGTCT | TCGCTTCGTC | CAGACCAACA | TCTCCCGCCT | CCTGCAGGAG | 240 |
| ACCTCCGAGC | AGCTGGTGGC | GCTGAAGCCC | TGGATCACTC | GCCAGAACTT | CTCCCGGTGC | 300 |
| CTGGAGCTGC | AGTGTGAGCC | CGACTCCTCA | ACCCTGGGCG | GTGGGTGAGG | AGGTGGGTCA | 360 |
| GGAGGTGGAT | CCGGAGGTGG | CACCCAGGAC | TGCTCCTTCC | AACACAGCCC | CATCTCCTCC | 420 |
| GACTTCGCTG | TCAAAATCCG | TGAGCTGTCT | GACTACCTGC | TTCAA      |            | 465 |

## (2) INFORMATION FOR SEQ ID NO:137:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 465 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:137:

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| GCCGCTCCA  | ACCTGCAGGA | CGAGGAGCTC | TGCGGGGGCC | TCTGGCGGCT | GGTCTGGCA  | 60  |
| CAGCGCTGGA | TGGAGCGGCT | CAAGACTGTC | GCTGGGTCCA | AGATGCAAGG | CTTGCTGGAG | 120 |
| CGCGTGAACA | CGGAGATACA | CTTTGTCAAC | AAATGTGCCT | TTCAGCCCCC | CCCCAGCTGT | 180 |
| CTTCGCTTCG | TCCAGACCAA | CATCTCCCGC | CTCCTGCAGG | AGACCTCCGA | GCAGCTGGTG | 240 |
| GCGCTGAAGC | CCTGGATCAC | TCGCCAGAAC | TTCTCCCGGT | GCCTGGAGCT | GCAGTGTGAG | 300 |
| CCCGACTCCT | CAACCCTGGG | CGGTGGGTCA | GGAGGTGGGT | CAGGAGGTGG | ATCCGGAGGT | 360 |
| GGCACCCAGG | ACTGCTCCTT | CCAACACAGC | CCCATCTCCT | CCGACTTCGC | TGTCAAAATC | 420 |
| CGTGAGCTGT | CTGACTACCT | GCTTCAAGAT | TACCCAGTCA | CCGTG      |            | 465 |

## (2) INFORMATION FOR SEQ ID NO:138:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 465 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:138:

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| GCCGTCGCTG | GGTCCAAGAT | GCAAGGCTTG | CTGGAGCGCG | TGAACACGGA | GATACACTTT | 60  |
| GTCACCAAAT | GTGCCTTTCA | GCCCCCCCCC | AGCTGTCTTC | GCTTCGTCCA | GACCAACATC | 120 |
| TCCCGCCTCC | TGCAGGAGAC | CTCCGAGCAG | CTGGTGGCGC | TGAAGCCCTG | GATCACTCGC | 180 |
| CAGAACTTCT | CCCGGTGCCT | GGAGCTGCAG | TGTCAGCCCG | ACTCCTCAAC | CCTGGGCGGT | 240 |
| GGGTGAGGAG | GTGGGTGAGG | AGGTGGATCC | GGAGGTGGCA | CCCAGGACTG | CTCCTTCCAA | 300 |
| CACAGCCCCA | TCTCTCCGA  | CTTCGTGTG  | AAAATCCGTG | AGCTGTCTGA | CTACCTGTCT | 360 |
| CAAGATTACC | CAGTCACCGT | GGCCTCCAAC | CTGCAGGACG | AGGAGCTCTG | CGGGGGCCTC | 420 |
| TGGCGGCTGG | TCCTGGCACA | GCGCTGGATG | GAGCGGTCTA | AGACT      |            | 465 |

## (2) INFORMATION FOR SEQ ID NO:139:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 465 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:139:

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| GCCTCCAAGA | TGCAAGGCTT | GCTGGAGCGC | GTGAACACGG | AGATACACTT | TGTCACCAAA | 60  |
| TGTGCCTTTT | AGCCCCCCCC | CAGCTGTCTT | CGCTTCGTCC | AGACCAACAT | CTCCCGCCTC | 120 |
| CTGCAGGAGA | CCTCCGAGCA | GCTGGTGGCG | CTGAAGCCCT | GGATCACTCG | CCAGAACTTC | 180 |
| TCCCGGTGCC | TGGAGCTGCA | GTGTCAGCCC | GACTCCTCAA | CCCTGGGCGG | TGGGTGAGGA | 240 |
| GGTGGGTGAG | GAGGTGGATC | CGGAGGTGGC | ACCCAGGACT | GCTCCTTCCA | ACACAGCCCC | 300 |
| ATCTCCTCCG | ACTTCGCTGT | CAAAATCCGT | GAGCTGTCTG | ACTACCTGCT | TCAAGATTAC | 360 |
| CCAGTCACCG | TGGCCTCCAA | CCTGCAGGAC | GAGGAGCTCT | GCGGGGGCCT | CTGGCGGCTG | 420 |
| GTCTTGCCAC | AGCGCTGGAT | GGAGCGGCTC | AAGACTGTCT | CTGGG      |            | 465 |

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## (2) INFORMATION FOR SEQ ID NO:140:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 465 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:140:

```

GCCCCCCCCA GCTGTCTTCG CTTCGTCCAG ACCAACATCT CCCGCCTCCT GCAGGAGACC      60
TCCGAGCAGC TGGTGGCGCT GAAGCCCTGG ATCACTCGCC AGAACTTCTC CCGGTGCCTG      120
GAGCTGCAGT GTCAGCCCGA CTCCTCAACC CTGGGCGGTG GGTCAAGGAGG TGGGTCAAGG      180
GGTGGATCCG GAGGTGGCAC CCAGGACTGC TCCTTCCAAC ACAGCCCCAT CTCCTCCGAC      240
TTCGTGTCA AAATCCGTGA GCTGTCTGAC TACCTGCTTC AAGATTACCC AGTCACCGTG      300
GCCTCCAACC TGCAGGACGA GGAGCTCTGC GGGGGCCTCT GGCGGCTGGT CCTGGCACAG      360
CGCTGGATGG AGCGGCTCAA GACTGTCGCT GGGTCCAAGA TGCAAGGCTT GCTGGAGCGC      420
GTGAACACGG AGATACACTT TGTACCAAAA TGTGCCTTTC AGCCC                      465

```

## (2) INFORMATION FOR SEQ ID NO:141:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 465 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:141:

```

GCCCGCTTCG TCCAGACCAA CATCTCCCGC CTCCTGCAGG AGACCTCCGA GCAGCTGGTG      60
GCGCTGAAGC CCTGGATCAC TCGCCAGAAC TTCTCCCGGT GCCTGGAGCT GCAGTGTACG      120
CCCGACTCCT CAACCCTGGG CGGTGGGTCA GGAGGTGGGT CAGGAGGTGG ATCCGGAGGT      180
GGCACCCAGG ACTGCTCCTT CCAACACAGC CCCATCTCCT CCGACTTCGC TGTCAAAATC      240
CGTGAGCTGT CTGACTACCT GCTTCAAGAT TACCCAGTCA CCGTGGCCTC CAACCTGCAG      300
GACGAGGAGC TCTGCGGGGG CCTCTGGCGG CTGGTCTGG CACAGCGCTG GATGGAGCGG      360
CTCAAGACTG TCCTGGGTC CAAGATGCAA GGCTTGTCTG AGCGCGTGAA CACGGAGATA      420
CACTTTGTCA CCAAAATGTGC CTTTCAGCCC CCCCCAGCT GTCTT                      465

```

## (2) INFORMATION FOR SEQ ID NO:142:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 465 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:142:

```

GCCACCAACA TCTCCCGCCT CCTGCAGGAG ACCTCCGAGC AGCTGGTGGC GCTGAAGCCC      60
TGGATCACTC GCCAGAACTT CTCCCGGTGC CTGGAGCTGC AGTGTGAGCC CGACTCCTCA      120
ACCCTGGGCG GTGGGTGAGG AGGTGGGTCA GGAGGTGGAT CCGGAGGTGG CACCCAGGAC      180
TGCTCCTTCC AACACAGCCC CATCTCCTCC GACTTCGCTG TCAAAATCCG TGAGCTGTCT      240
GACTACCTGC TTCAAGATTA CCCAGTCACC GTGGCCTCCA ACCTGCAGGA CGAGGAGCTC      300
TGCGGGGGCC TCTGGCGGCT GGTCTGGCA CAGCGCTGGA TGGAGCGGCT CAAGACTGTC      360
GCTGGGTCCA AGATGCAAGG CTTGCTGGAG CGCGTGAACA CGGAGATACA CTTTGTCCAC      420
AAATGTGCCT TTCAGCCCCC CCCAGCTGT CTTGCTTCG TCCAG                      465

```

## (2) INFORMATION FOR SEQ ID NO:143:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 134 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:143:

```

Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala
 1           5           10           15
Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val
          20           25           30

```

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```

Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu Cys Gly Gly Leu Trp
      35          40          45
Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg Leu Lys Thr Val Ala
      50          55          60
Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile His
      65          70          75          80
Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Pro Ser Cys Leu Arg Phe
      85          90          95
Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu
      100          105          110
Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu
      115          120          125
Glu Leu Gln Cys Gln Pro
      130

```

## (2) INFORMATION FOR SEQ ID NO:144:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 139 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:144:

```

Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala
  1          5          10          15
Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val
      20          25          30
Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu Cys Gly Gly Leu Trp
      35          40          45
Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg Leu Lys Thr Val Ala
      50          55          60
Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile His
      65          70          75          80
Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Pro Ser Cys Leu Arg Phe
      85          90          95
Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu
      100          105          110
Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu
      115          120          125
Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu
      130          135

```

## (2) INFORMATION FOR SEQ ID NO:145:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 209 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: None

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:145:

```

Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala
  1          5          10          15
Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val
      20          25          30
Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu Cys Gly Gly Leu Trp
      35          40          45
Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg Leu Lys Thr Val Ala
      50          55          60
Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile His
      65          70          75          80
Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Pro Ser Cys Leu Arg Phe
      85          90          95
Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu
      100          105          110
Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu
      115          120          125
Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Pro Pro Pro Trp Ser
      130          135          140
Pro Arg Pro Leu Glu Ala Thr Ala Pro Thr Ala Pro Gln Pro Pro Leu

```

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145                      150                      155                      160  
 Leu Leu Leu Leu Leu Pro Val Gly Leu Leu Leu Ala Ala Ala  
                          165                      170                      175  
 Trp Cys Leu His Trp Gln Arg Thr Arg Arg Arg Thr Pro Arg Pro Gly  
                          180                      185                      190  
 Glu Gln Val Pro Pro Val Pro Ser Pro Gln Asp Leu Leu Val Glu  
                          195                      200                      205  
 His

## (2) INFORMATION FOR SEQ ID NO:146:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 402 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:146:

|             |            |            |            |            |            |     |
|-------------|------------|------------|------------|------------|------------|-----|
| ACCCAGGACT  | GCTCCTTCCA | ACACAGCCCC | ATCTCCTCCG | ACTTCGCTGT | CAAAATCCGT | 60  |
| GAGCTGTCTG  | ACTACCTGCT | TCAAGATTAC | CCAGTCACCG | TGGCCTCCAA | CCTGCAGGAC | 120 |
| GAGGAGCTCT  | GCGGGGGCCT | CTGGCGGCTG | GTCTTGGCAC | AGCGCTGGAT | GGAGCGGCTC | 180 |
| AAGACTGTCTG | CTGGGTCCAA | GATGCAAGGC | TTGCTGGAGC | GCGTGAACAC | GGAGATACAC | 240 |
| TTTGTCACCA  | AATGTGCCTT | TCAGCCCCCC | CCCAGCTGTC | TTCGCTTCGT | CCAGACCAAC | 300 |
| ATCTCCCGCC  | TCCTGCAGGA | GACCTCCGAG | CAGCTGGTGG | CGCTGAAGCC | CTGGATCACT | 360 |
| CGCCAGAACT  | TCTCCCGGTG | CCTGGAGCTG | CAGTGTACAG | CC         |            | 402 |

## (2) INFORMATION FOR SEQ ID NO:147:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 630 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:147:

|             |            |            |            |            |            |     |
|-------------|------------|------------|------------|------------|------------|-----|
| ACCCAGGACT  | GCTCCTTCCA | ACACAGCCCC | ATCTCCTCCG | ACTTCGCTGT | CAAAATCCGT | 60  |
| GAGCTGTCTG  | ACTACCTGCT | TCAAGATTAC | CCAGTCACCG | TGGCCTCCAA | CCTGCAGGAC | 120 |
| GAGGAGCTCT  | GCGGGGGCCT | CTGGCGGCTG | GTCTTGGCAC | AGCGCTGGAT | GGAGCGGCTC | 180 |
| AAGACTGTCTG | CTGGGTCCAA | GATGCAAGGC | TTGCTGGAGC | GCGTGAACAC | GGAGATACAC | 240 |
| TTTGTCACCA  | AATGTGCCTT | TCAGCCCCCC | CCCAGCTGTC | TTCGCTTCGT | CCAGACCAAC | 300 |
| ATCTCCCGCC  | TCCTGCAGGA | GACCTCCGAG | CAGCTGGTGG | CGCTGAAGCC | CTGGATCACT | 360 |
| CGCCAGAACT  | TCTCCCGGTG | CCTGGAGCTG | CAGTGTACAG | CCGACTCCTC | AACCTTGCCA | 420 |
| CCCCCATGGA  | GTCCCCGGCC | CCTGGAGGCC | ACAGCCCCGA | CAGCCCCGCA | GCCCCCTCTG | 480 |
| CTCCTCCTAC  | TGCTGCTGCC | CGTGGGCCTC | CTGCTGCTGG | CCGCTGCCTG | GTGCCTGCAC | 540 |
| TGGCAGAGGA  | CGCGGCGGAG | GACACCCCGC | CCTGGGGAGC | AGGTGCCCCC | CGTCCCCAGT | 600 |
| CCCCAGGACC  | TGCTGCTTGT | GGAGCACTGA |            |            |            | 630 |

## (2) INFORMATION FOR SEQ ID NO:148:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:148:

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Gly | Gly | Ser | Gly | Gly | Gly | Ser | Gly | Gly | Gly | Ser | Gly | Gly | Gly | Ser |
| 1   |     |     |     | 5   |     |     |     | 10  |     |     |     |     |     | 15  |     |
| Gly | Gly | Gly | Ser | Gly | Gly | Gly | Ser | Gly | Gly | Gly | Ser | Gly |     |     |     |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     |     |     |     |

## (2) INFORMATION FOR SEQ ID NO:149:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 21 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:149:

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Pro | Pro | Trp | Ser | Pro | Arg | Pro | Leu | Gly | Ala | Thr | Ala | Pro | Thr | Ala |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |
| Gly | Gln | Pro | Pro | Leu |     |     |     |     |     |     |     |     |     |     |     |
|     |     |     |     | 20  |     |     |     |     |     |     |     |     |     |     |     |

(2) INFORMATION FOR SEQ ID NO:150:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:150:

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Pro | Pro | Trp | Ser | Pro | Arg | Pro | Leu | Gly | Ala | Thr | Ala | Pro | Thr |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |

(2) INFORMATION FOR SEQ ID NO:151:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:151:

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Glu | Thr | Val | Phe | His | Arg | Val | Ser | Gln | Asp | Gly | Leu | Leu | Thr | Ser |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

## WHAT IS CLAIMED IS:

1. A human<sup>\*</sup> flt-3 receptor agonist polypeptide,  
comprising a modified flt-3 ligand amino acid sequence  
5 of the Formula:

```

      ThrGlnAspCysSerPheGlnHisSerProIleSerSerAspPheAlaValLysIleArg
                                10                                20
10  GluLeuSerAspTyrLeuLeuGlnAspTyrProValThrValAlaSerAsnLeuGlnAsp
                                30                                40
      GluGluLeuCysGlyGlyLeuTrpArgLeuValLeuAlaGlnArgTrpMetGluArgLeu
                                50                                60
15  LysThrValAlaGlySerLysMetGlnGlyLeuLeuGluArgValAsnThrGluIleHis
                                70                                80
      PheValThrLysCysAlaPheGlnProProProSerCysLeuArgPheValGlnThrAsn
                                90                                100
20  IleSerArgLeuLeuGlnGluThrSerGluGlnLeuValAlaLeuLysProTrpIleThr
                                110                               120
      ArgGlnAsnPheSerArgCysLeuGluLeuGlnCysGlnProAspSerSerThrLeu
                                130                               SEQ ID NO:144
25

```

wherein 1-7 amino acids are optionally deleted from the  
C-terminus of said flt-3 receptor agonist polypeptide of  
30 SEQ ID NO:144;

wherein the N-terminus is joined to the C-terminus  
directly or through a linker capable of joining the N-  
terminus to the C-terminus and having new C- and N-  
35 termini at amino acids;

|       |       |                   |
|-------|-------|-------------------|
| 28-29 | 42-43 | 93-94             |
| 29-30 | 64-65 | 94-95             |
| 30-31 | 65-66 | 95-96             |
| 31-32 | 66-67 | 96-97             |
| 32-33 | 86-87 | 97-98             |
| 34-35 | 87-88 | 98-99             |
| 36-37 | 88-89 | 99-100            |
| 37-38 | 89-90 | 100-101           |
| 38-39 | 90-91 | 101-102           |
| 39-40 | 91-92 | 102-103           |
| 40-41 | 92-93 | respectively; and |

41-42

additionally said new N-terminus of said flt-3 receptor agonist polypeptide is optionally immediately preceded by (methionine<sup>-1</sup>), (alanine<sup>-1</sup>) or (methionine<sup>-2</sup>, alanine<sup>-1</sup>).

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2. The flt-3 receptor agonist polypeptide, as recited in claim 1, wherein said linker is selected from the group consisting of;

GlyGlyGlySer SEQ ID NO:38;  
 10 GlyGlyGlySerGlyGlyGlySer SEQ ID NO:39;  
 GlyGlyGlySerGlyGlyGlySerGlyGlyGlySer SEQ ID NO:40;  
 SerGlyGlySerGlyGlySer SEQ ID NO:41;  
 GluPheGlyAsnMet SEQ ID NO:42;  
 GluPheGlyGlyAsnMet SEQ ID NO:43;  
 15 GluPheGlyGlyAsnGlyGlyAsnMet SEQ ID NO:44;  
 GlyGlySerAspMetAlaGly SEQ ID NO:45;  
 SerGlyGlyAsnGly SEQ ID NO:46;  
 SerGlyGlyAsnGlySerGlyGlyAsnGly SEQ ID NO:47;  
 SerGlyGlyAsnGlySerGlyGlyAsnGlySerGlyGlyAsnGly SEQ ID NO:48;  
 20 SerGlyGlySerGlySerGlyGlySerGly SEQ ID NO:49;  
 SerGlyGlySerGlySerGlyGlySerGlySerGlyGlySerGly SEQ ID NO:50;  
 GlyGlyGlySerGlyGly SEQ ID NO:51;  
 GlyGlyGlySerGlyGlyGly SEQ ID NO:52;  
 GlyGlyGlySerGlyGlyGlySerGlyGly SEQ ID NO:53;  
 25 GlyGlyGlySerGlyGlyGlySerGlyGlyGlySerGly SEQ ID NO:54;  
 GlyGlyGlySerGlyGlyGlySerGlyGlyGlySerGlyGlyGly SEQ ID NO:55;  
 GlyGlyGlySerGlyGlyGlySerGlyGlyGlySerGlyGlyGlySerGly  
 GlyGlySerGly SEQ ID NO:56;  
 GlyGlyGlySerGlyGlyGlySerGlyGlyGlySerGlyGlyGlySerGly  
 30 GlyGlySerGlyGlyGlySerGlyGlyGlySerGly SEQ ID NO:148;  
 ProProProTrpSerProArgProLeuGlyAlaThrAlaProThrAlaGly  
 GlnProProLeu SEQ ID NO:149;  
 ProProProTrpSerProArgProLeuGlyAlaThrAlaProThr SEQ ID NO:150;  
 and  
 35 ValGluThrValPheHisArgValSerGlnAspGlyLeuLeuThrSer SEQ ID  
 NO:151.

3. The flt-3 receptor agonist polypeptide, as  
recited in claim 1, selected from the group consisting  
of;

AlaAspGluGluLeuCysGlyGlyLeuTrpArgLeuValLeuAlaGlnArgTrpMETGlu  
ArgLeuLysThrValAlaGlySerLysMETGlnGlyLeuLeuGluArgValAsnThrGlu  
IleHisPheValThrLysCysAlaPheGlnProProProSerCysLeuArgPheValGln  
10 ThrAsnIleSerArgLeuLeuGlnGluThrSerGluGlnLeuValAlaLeuLysProTrp  
IleThrArgGlnAsnPheSerArgCysLeuGluLeuGlnCysGlnProAspSerSerThr  
LeuSerGlyGlyAsnGlySerGlyGlyAsnGlySerGlyGlyAsnGlyThrGlnAspCys  
SerPheGlnHisSerProIleSerSerAspPheAlaValLysIleArgGluLeuSerAsp  
TyrLeuLeuGlnAspTyrProValThrValAlaSerAsnLeuGln SEQ ID NO:8;

15  
AlaAspGluGluLeuCysGlyGlyLeuTrpArgLeuValLeuAlaGlnArgTrpMETGlu  
ArgLeuLysThrValAlaGlySerLysMETGlnGlyLeuLeuGluArgValAsnThrGlu  
IleHisPheValThrLysCysAlaPheGlnProProProSerCysLeuArgPheValGln  
20 ThrAsnIleSerArgLeuLeuGlnGluThrSerGluGlnLeuValAlaLeuLysProTrp  
IleThrArgGlnAsnPheSerArgCysLeuGluLeuGlnCysGlnProAspSerSerThr  
LeuSerGlyGlyAsnGlySerGlyGlyAsnGlyThrGlnAspCysSerPheGlnHisSer  
ProIleSerSerAspPheAlaValLysIleArgGluLeuSerAspTyrLeuLeuGlnAsp  
TyrProValThrValAlaSerAsnLeuGln SEQ ID NO:9;

25  
AlaAspGluGluLeuCysGlyGlyLeuTrpArgLeuValLeuAlaGlnArgTrpMETGlu  
ArgLeuLysThrValAlaGlySerLysMETGlnGlyLeuLeuGluArgValAsnThrGlu  
IleHisPheValThrLysCysAlaPheGlnProProProSerCysLeuArgPheValGln  
30 ThrAsnIleSerArgLeuLeuGlnGluThrSerGluGlnLeuValAlaLeuLysProTrp  
IleThrArgGlnAsnPheSerArgCysLeuGluLeuGlnCysGlnProAspSerSerThr  
LeuSerGlyGlyAsnGlyThrGlnAspCysSerPheGlnHisSerProIleSerSerAsp  
PheAlaValLysIleArgGluLeuSerAspTyrLeuLeuGlnAspTyrProValThrVal  
AlaSerAsnLeuGln SEQ ID NO:10;

35  
AlaSerLysMETGlnGlyLeuLeuGluArgValAsnThrGluIleHisPheValThrLys  
CysAlaPheGlnProProProSerCysLeuArgPheValGlnThrAsnIleSerArgLeu  
LeuGlnGluThrSerGluGlnLeuValAlaLeuLysProTrpIleThrArgGlnAsnPhe  
40 SerArgCysLeuGluLeuGlnCysGlnProAspSerSerThrLeuSerGlyGlyAsnGly  
SerGlyGlyAsnGlySerGlyGlyAsnGlyThrGlnAspCysSerPheGlnHisSerPro  
IleSerSerAspPheAlaValLysIleArgGluLeuSerAspTyrLeuLeuGlnAspTyr  
ProValThrValAlaSerAsnLeuGlnAspGluGluLeuCysGlyGlyLeuTrpArgLeu  
ValLeuAlaGlnArgTrpMETGluArgLeuLysThrValAlaGly SEQ ID NO:11;

45  
AlaSerLysMETGlnGlyLeuLeuGluArgValAsnThrGluIleHisPheValThrLys  
CysAlaPheGlnProProProSerCysLeuArgPheValGlnThrAsnIleSerArgLeu  
LeuGlnGluThrSerGluGlnLeuValAlaLeuLysProTrpIleThrArgGlnAsnPhe  
50 SerArgCysLeuGluLeuGlnCysGlnProAspSerSerThrLeuSerGlyGlyAsnGly  
SerGlyGlyAsnGlyThrGlnAspCysSerPheGlnHisSerProIleSerSerAspPhe  
AlaValLysIleArgGluLeuSerAspTyrLeuLeuGlnAspTyrProValThrValAla  
SerAsnLeuGlnAspGluGluLeuCysGlyGlyLeuTrpArgLeuValLeuAlaGlnArg  
TrpMETGluArgLeuLysThrValAlaGly SEQ ID NO:12;

AlaSerLysMETGlnGlyLeuLeuGluArgValAsnThrGluIleHisPheValThrLys  
 CysAlaPheGlnProProProSerCysLeuArgPheValGlnThrAsnIleSerArgLeu  
 5 LeuGlnGluThrSerGluGlnLeuValAlaLeuLysProTrpIleThrArgGlnAsnPhe  
 SerArgCysLeuGluLeuGlnCysGlnProAspSerSerThrLeuSerGlyGlyAsnGly  
 ThrGlnAspCysSerPheGlnHisSerProIleSerSerAspPheAlaValLysIleArg  
 GluLeuSerAspTyrLeuLeuGlnAspTyrProValThrValAlaSerAsnLeuGlnAsp  
 GluGluLeuCysGlyGlyLeuTrpArgLeuValLeuAlaGlnArgTrpMETGluArgLeu  
 10 LysThrValAlaGly SEQ ID NO:13;

AlaProProSerCysLeuArgPheValGlnThrAsnIleSerArgLeuLeuGlnGluThr  
 SerGluGlnLeuValAlaLeuLysProTrpIleThrArgGlnAsnPheSerArgCysLeu  
 15 GluLeuGlnCysGlnProAspSerSerThrLeuSerGlyGlyAsnGlySerGlyGlyAsn  
 GlySerGlyGlyAsnGlyThrGlnAspCysSerPheGlnHisSerProIleSerSerAsp  
 PheAlaValLysIleArgGluLeuSerAspTyrLeuLeuGlnAspTyrProValThrVal  
 AlaSerAsnLeuGlnAspGluGluLeuCysGlyGlyLeuTrpArgLeuValLeuAlaGln  
 ArgTrpMETGluArgLeuLysThrValAlaGlySerLysMETGlnGlyLeuLeuGluArg  
 20 ValAsnThrGluIleHisPheValThrLysCysAlaPheGlnPro SEQ ID NO:14;

AlaProProSerCysLeuArgPheValGlnThrAsnIleSerArgLeuLeuGlnGluThr  
 SerGluGlnLeuValAlaLeuLysProTrpIleThrArgGlnAsnPheSerArgCysLeu  
 25 GluLeuGlnCysGlnProAspSerSerThrLeuSerGlyGlyAsnGlySerGlyGlyAsn  
 GlyThrGlnAspCysSerPheGlnHisSerProIleSerSerAspPheAlaValLysIle  
 ArgGluLeuSerAspTyrLeuLeuGlnAspTyrProValThrValAlaSerAsnLeuGln  
 AspGluGluLeuCysGlyGlyLeuTrpArgLeuValLeuAlaGlnArgTrpMETGluArg  
 LeuLysThrValAlaGlySerLysMETGlnGlyLeuLeuGluArgValAsnThrGluIle  
 30 HisPheValThrLysCysAlaPheGlnPro SEQ ID NO:15;

AlaProProSerCysLeuArgPheValGlnThrAsnIleSerArgLeuLeuGlnGluThr  
 SerGluGlnLeuValAlaLeuLysProTrpIleThrArgGlnAsnPheSerArgCysLeu  
 35 GluLeuGlnCysGlnProAspSerSerThrLeuSerGlyGlyAsnGlyThrGlnAspCys  
 SerPheGlnHisSerProIleSerSerAspPheAlaValLysIleArgGluLeuSerAsp  
 TyrLeuLeuGlnAspTyrProValThrValAlaSerAsnLeuGlnAspGluGluLeuCys  
 GlyGlyLeuTrpArgLeuValLeuAlaGlnArgTrpMETGluArgLeuLysThrValAla  
 GlySerLysMETGlnGlyLeuLeuGluArgValAsnThrGluIleHisPheValThrLys  
 40 CysAlaPheGlnPro SEQ ID NO:16;

AlaAspTyrProValThrValAlaSerAsnLeuGlnAspGluGluLeuCysGlyGlyLeu  
 TrpArgLeuValLeuAlaGlnArgTrpMetGluArgLeuLysThrValAlaGlySerLys  
 45 MetGlnGlyLeuLeuGluArgValAsnThrGluIleHisPheValThrLysCysAlaPhe  
 GlnProProProSerCysLeuArgPheValGlnThrAsnIleSerArgLeuLeuGlnGlu  
 ThrSerGluGlnLeuValAlaLeuLysProTrpIleThrArgGlnAsnPheSerArgCys  
 LeuGluLeuGlnCysGlnProAspSerSerThrLeuGlyGlyGlySerGlyGlyGlySer  
 GlyGlyGlySerGlyGlyGlyThrGlnAspCysSerPheGlnHisSerProIleSerSer  
 50 AspPheAlaValLysIleArgGluLeuSerAspTyrLeuLeuGln SEQ ID NO:31;

AlaAlaSerAsnLeuGlnAspGluGluLeuCysGlyGlyLeuTrpArgLeuValLeuAla  
 GlnArgTrpMetGluArgLeuLysThrValAlaGlySerLysMetGlnGlyLeuLeuGlu  
 55 ArgValAsnThrGluIleHisPheValThrLysCysAlaPheGlnProProProSerCys  
 LeuArgPheValGlnThrAsnIleSerArgLeuLeuGlnGluThrSerGluGlnLeuVal

AlaLeuLysProTrpIleThrArgGlnAsnPheSerArgCysLeuGluLeuGlnCysGln  
 ProAspSerSerThrLeuGlyGlyGlySerGlyGlyGlySerGlyGlyGlySerGlyGly  
 GlyThrGlnAspCysSerPheGlnHisSerProIleSerSerAspPheAlaValLysIle  
 ArgGluLeuSerAspTyrLeuLeuGlnAspTyrProValThrVal SEQ ID NO:32;  
 5

AlaValAlaGlySerLysMetGlnGlyLeuLeuGluArgValAsnThrGluIleHisPhe  
 ValThrLysCysAlaPheGlnProProProSerCysLeuArgPheValGlnThrAsnIle  
 SerArgLeuLeuGlnGluThrSerGluGlnLeuValAlaLeuLysProTrpIleThrArg  
 GlnAsnPheSerArgCysLeuGluLeuGlnCysGlnProAspSerSerThrLeuGlyGly  
 GlySerGlyGlyGlySerGlyGlyGlySerGlyGlyGlyThrGlnAspCysSerPheGln  
 HisSerProIleSerSerAspPheAlaValLysIleArgGluLeuSerAspTyrLeuLeu  
 GlnAspTyrProValThrValAlaSerAsnLeuGlnAspGluGluLeuCysGlyGlyLeu  
 TrpArgLeuValLeuAlaGlnArgTrpMetGluArgLeuLysThr SEQ ID NO:33;  
 10 15

AlaSerLysMetGlnGlyLeuLeuGluArgValAsnThrGluIleHisPheValThrLys  
 CysAlaPheGlnProProProSerCysLeuArgPheValGlnThrAsnIleSerArgLeu  
 LeuGlnGluThrSerGluGlnLeuValAlaLeuLysProTrpIleThrArgGlnAsnPhe  
 SerArgCysLeuGluLeuGlnCysGlnProAspSerSerThrLeuGlyGlyGlySerGly  
 GlyGlySerGlyGlyGlySerGlyGlyGlyThrGlnAspCysSerPheGlnHisSerPro  
 IleSerSerAspPheAlaValLysIleArgGluLeuSerAspTyrLeuLeuGlnAspTyr  
 ProValThrValAlaSerAsnLeuGlnAspGluGluLeuCysGlyGlyLeuTrpArgLeu  
 ValLeuAlaGlnArgTrpMetGluArgLeuLysThrValAlaGly SEQ ID NO:34;  
 20 25

AlaProProSerCysLeuArgPheValGlnThrAsnIleSerArgLeuLeuGlnGluThr  
 SerGluGlnLeuValAlaLeuLysProTrpIleThrArgGlnAsnPheSerArgCysLeu  
 GluLeuGlnCysGlnProAspSerSerThrLeuGlyGlyGlySerGlyGlyGlySerGly  
 GlyGlySerGlyGlyGlyThrGlnAspCysSerPheGlnHisSerProIleSerSerAsp  
 PheAlaValLysIleArgGluLeuSerAspTyrLeuLeuGlnAspTyrProValThrVal  
 AlaSerAsnLeuGlnAspGluGluLeuCysGlyGlyLeuTrpArgLeuValLeuAlaGln  
 ArgTrpMetGluArgLeuLysThrValAlaGlySerLysMetGlnGlyLeuLeuGluArg  
 ValAsnThrGluIleHisPheValThrLysCysAlaPheGlnPro SEQ ID NO:35;  
 30 35

AlaArgPheValGlnThrAsnIleSerArgLeuLeuGlnGluThrSerGluGlnLeuVal  
 AlaLeuLysProTrpIleThrArgGlnAsnPheSerArgCysLeuGluLeuGlnCysGln  
 ProAspSerSerThrLeuGlyGlyGlySerGlyGlyGlySerGlyGlyGlySerGlyGly  
 GlyThrGlnAspCysSerPheGlnHisSerProIleSerSerAspPheAlaValLysIle  
 ArgGluLeuSerAspTyrLeuLeuGlnAspTyrProValThrValAlaSerAsnLeuGln  
 AspGluGluLeuCysGlyGlyLeuTrpArgLeuValLeuAlaGlnArgTrpMetGluArg  
 LeuLysThrValAlaGlySerLysMetGlnGlyLeuLeuGluArgValAsnThrGluIle  
 HisPheValThrLysCysAlaPheGlnProProProSerCysLeu SEQ ID NO:36;  
 40 45

AlaThrAsnIleSerArgLeuLeuGlnGluThrSerGluGlnLeuValAlaLeuLysPro  
 TrpIleThrArgGlnAsnPheSerArgCysLeuGluLeuGlnCysGlnProAspSerSer  
 ThrLeuGlyGlyGlySerGlyGlyGlySerGlyGlyGlySerGlyGlyGlyThrGlnAsp  
 CysSerPheGlnHisSerProIleSerSerAspPheAlaValLysIleArgGluLeuSer  
 AspTyrLeuLeuGlnAspTyrProValThrValAlaSerAsnLeuGlnAspGluGluLeu  
 CysGlyGlyLeuTrpArgLeuValLeuAlaGlnArgTrpMetGluArgLeuLysThrVal  
 AlaGlySerLysMetGlnGlyLeuLeuGluArgValAsnThrGluIleHisPheValThr  
 LysCysAlaPheGlnProProProSerCysLeuArgPheValGln SEQ ID NO:37.  
 50 55

4. A nucleic acid molecule, comprising a sequence encoding the flt-3 receptor agonist polypeptide of claim 1.

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5. A nucleic acid molecule, comprising a sequence encoding the flt-3 receptor agonist polypeptide of claim 2.

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6. A nucleic acid molecule, comprising a sequence encoding the flt-3 receptor agonist polypeptide of claim 3.

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7. A nucleic acid molecule, comprising a sequence encoding the flt-3 receptor agonist polypeptide of claim 6, selected from the group consisting of:

20 GCCGACGAGGAGCTCTGCGGGGGCCTCTGGCGGCTGGTCCTGGCACAGCG  
CTGGATGGAGCGGCTCAAGACTGTCGCTGGGTCCAAGATGCAAGGCTTGC  
TGGAGCGCGTGAACACGGAGATACACTTTGTACACAAATGTGCCTTTTCAG  
CCCCCCCCCAGCTGTCTTCGCTTCGTCCAGACCAACATCTCCCGCCTCCT  
GCAGGAGACCTCCGAGCAGCTGGTGGCGCTGAAGCCCTGGATCACTCGCC  
AGAACTTCTCCCGGTGCCTGGAGCTGCAGTGTGAGCCCGACTCCTCAACC  
25 CTGTCTGGAGGTAACGGATCCGGTGGCAATGGGAGCGGCGGAAATGGAAC  
CCAGGACTGCTCCTTCCAACACAGCCCCATCTCCTCCGACTTCGCTGTCA  
AAATCCGTGAGCTGTCTGACTACCTGCTTCAAGATTACCCAGTCACCGTG  
GCCTCCAACCTGCAG SEQ ID NO:113;

30 GCCGACGAGGAGCTCTGCGGGGGCCTCTGGCGGCTGGTCCTGGCACAGCG  
CTGGATGGAGCGGCTCAAGACTGTCGCTGGGTCCAAGATGCAAGGCTTGC  
TGGAGCGCGTGAACACGGAGATACACTTTGTACACAAATGTGCCTTTTCAG  
CCCCCCCCCAGCTGTCTTCGCTTCGTCCAGACCAACATCTCCCGCCTCCT  
GCAGGAGACCTCCGAGCAGCTGGTGGCGCTGAAGCCCTGGATCACTCGCC  
35 AGAACTTCTCCCGGTGCCTGGAGCTGCAGTGTGAGCCCGACTCCTCAACC  
CTGTGAGGCGGTAACGGCAGTGGAGGTAATGGCACCCAGGACTGCTCCTT  
CCAACACAGCCCCATCTCCTCCGACTTCGCTGTCAAAATCCGTGAGCTGT  
CTGACTACCTGCTTCAAGATTACCCAGTCACCGTGGCCTCCAACCTGCAG  
SEQ ID NO:114;

40

45 GCCGACGAGGAGCTCTGCGGGGGCCTCTGGCGGCTGGTCCTGGCACAGCG  
CTGGATGGAGCGGCTCAAGACTGTCGCTGGGTCCAAGATGCAAGGCTTGC  
TGGAGCGCGTGAACACGGAGATACACTTTGTACACAAATGTGCCTTTTCAG  
CCCCCCCCCAGCTGTCTTCGCTTCGTCCAGACCAACATCTCCCGCCTCCT  
GCAGGAGACCTCCGAGCAGCTGGTGGCGCTGAAGCCCTGGATCACTCGCC  
AGAACTTCTCCCGGTGCCTGGAGCTGCAGTGTGAGCCCGACTCCTCAACC  
CTGTCTGGCGGCAACGGCACCCAGGACTGCTCCTTCCAACACAGCCCCAT  
CTCCTCCGACTTCGCTGTCAAAATCCGTGAGCTGTCTGACTACCTGCTTC

AAGATTACCCAGTCACCGTGGCCTCCAACCTGCAG SEQ ID NO:115;

5 GCCTCCAAGATGCAAGGCTTGCTGGAGCGCGTGAACACGGAGATACACTT  
 TGTCACCAAATGTGCCTTTCAGCCCCCCCCCAGCTGTCTTCGCTTCGTCC  
 AGACCAACATCTCCCGCCTCCTGCAGGAGACCTCCGAGCAGCTGGTGGCG  
 CTGAAGCCCTGGATCACTCGCCAGAACTTCTCCCGGTGCCTGGAGCTGCA  
 GTGTGAGCCCGACTCCTCAACCCCTGTCTGGAGGTAACGGATCCGGTGGCA  
 ATGGGAGCGGCGGAAATGGAACCCAGGACTGCTCCTTCCAACACAGCCCC  
 10 ATCTCCTCCGACTTCGCTGTCAAAATCCGTGAGCTGTCTGACTACCTGCT  
 TCAAGATTACCCAGTCACCGTGGCCTCCAACCTGCAGGACGAGGAGCTCT  
 GCGGGGGCCTCTGGCGGCTGGTCCTGGCACAGCGCTGGATGGAGCGGCTC  
 AAGACTGTGCTGGG SEQ ID NO:116;

15 GCCTCCAAGATGCAAGGCTTGCTGGAGCGCGTGAACACGGAGATACACTT  
 TGTCACCAAATGTGCCTTTCAGCCCCCCCCCAGCTGTCTTCGCTTCGTCC  
 AGACCAACATCTCCCGCCTCCTGCAGGAGACCTCCGAGCAGCTGGTGGCG  
 CTGAAGCCCTGGATCACTCGCCAGAACTTCTCCCGGTGCCTGGAGCTGCA  
 20 GTGTGAGCCCGACTCCTCAACCCCTGTCTGGAGGTAACGGATCCGGAGGTA  
 ATGGCAGCCAGGACTGCTCCTTCCAACACAGCCCCATCTCCTCCGACTTC  
 GCTGTCAAAATCCGTGAGCTGTCTGACTACCTGCTTCAAGATTACCCAGT  
 CACCGTGGCCTCCAACCTGCAGGACGAGGAGCTCTGCGGGGGCCTCTGGC  
 GGCTGGTCCTGGCACAGCGCTGGATGGAGCGGCTCAAGACTGTGCTGGG  
 25 SEQ ID NO:117;

GCCTCCAAGATGCAAGGCTTGCTGGAGCGCGTGAACACGGAGATACACTT  
 TGTCACCAAATGTGCCTTTCAGCCCCCCCCCAGCTGTCTTCGCTTCGTCC  
 30 AGACCAACATCTCCCGCCTCCTGCAGGAGACCTCCGAGCAGCTGGTGGCG  
 CTGAAGCCCTGGATCACTCGCCAGAACTTCTCCCGGTGCCTGGAGCTGCA  
 GTGTGAGCCCGACTCCTCAACCCCTGTCTGGCGGCAACGGCACGAGGACT  
 GCTCCTTCCAACACAGCCCCATCTCCTCCGACTTCGCTGTCAAAATCCGT  
 GAGCTGTCTGACTACCTGCTTCAAGATTACCCAGTCACCGTGGCCTCCAA  
 35 CCTGCAGGACGAGGAGCTCTGCGGGGGCCTCTGGCGGCTGGTCCTGGCAC  
 AGCGCTGGATGGAGCGGCTCAAGACTGTGCTGGG SEQ ID NO:118;

GCCTCCAAGATGCAAGGCTTGCTGGAGCGCGTGAACACGGAGATACACTT  
 TGTCACCAAATGTGCCTTTCAGCCCCCCCCCAGCTGTCTTCGCTTCGTCC  
 40 AGACCAACATCTCCCGCCTCCTGCAGGAGACCTCCGAGCAGCTGGTGGCG  
 CTGAAGCCCTGGATCACTCGCCAGAACTTCTCCCGGTGCCTGGAGCTGCA  
 GTGTGAGCCCGACTCCTCAACCCCTGTCTGGCGGCAACGGCACGAGGACT  
 GCTCCTTCCAACACAGCCCCATCTCCTCCGACTTCGCTGTCAAAATCCGT  
 GAGCTGTCTGACTACCTGCTTCAAGATTACCCAGTCACCGTGGCCTCCAA  
 45 CCTGCAGGACGAGGAGCTCTGCGGGGGCCTCTGGCGGCTGGTCCTGGCAC  
 AGCGCTGGATGGAGCGGCTCAAGACTGTGCTGGG SEQ ID NO:119;

GCCTCCAAGATGCAAGGCTTGCTGGAGCGCGTGAACACGGAGATACACTT  
 TGTCACCAAATGTGCCTTTCAGCCCCCCCCCAGCTGTCTTCGCTTCGTCC  
 50 AGACCAACATCTCCCGCCTCCTGCAGGAGACCTCCGAGCAGCTGGTGGCG  
 CTGAAGCCCTGGATCACTCGCCAGAACTTCTCCCGGTGCCTGGAGCTGCA  
 GTGTGAGCCCGACTCCTCAACCCCTGTCTGGCGGCAACGGCACGAGGACT  
 GCTCCTTCCAACACAGCCCCATCTCCTCCGACTTCGCTGTCAAAATCCGT  
 GAGCTGTCTGACTACCTGCTTCAAGATTACCCAGTCACCGTGGCCTCCAA  
 55 CCTGCAGGACGAGGAGCTCTGCGGGGGCCTCTGGCGGCTGGTCCTGGCAC  
 AGCGCTGGATGGAGCGGCTCAAGACTGTGCTGGG SEQ ID NO:120;

GATGGAGCGGCTCAAGACTGTCGCTGGGTCCAAGATGCAAGGCTTGCTGG  
AGCGCGTGAACACGGAGATACACTTTGTACCAAATGTGCCTTTCAGCCC  
SEQ ID NO:120;

5

5 GCGGGGGGAGCTGTCTTCGCTTCGTCCAGACCAACATCTCCCGCCTCCT  
GCAGGAGACCTCCGAGCAGCTGGTGGCGCTGAAGCCCTGGATCACTCGCC  
AGAATTCTCCCGGTGCCTGGAGCTGCAGTGTGAGCCCGACTCCTCAACC  
10 CTGTCTGGCGGCAACGGCACGCAGGACTGCTCCTTCCAACACAGCCCCAT  
CTCCTCCGACTTCGCTGTCAAAATCCGTGAGCTGTCTGACTACCTGCTTC  
AAGATTACCCAGTCACCGTGGCCTCCAACCTGCAGGACGAGGAGCTCTGC  
GGGGGCCCTCTGGCGGCTGGTCTTGGCACAGCGCTGGATGGAGCGGCTCAA  
GACTGTCGCTGGGTCCAAGATGCAAGGCTTGCTGGAGCGCGTGAACACGG  
AGATACACTTTGTACCAAATGTGCCTTTCAGCCC SEQ ID NO:121;

15

GCCGATTACCCAGTCACCGTGGCCTCCAACCTGCAGGACGAGGAGCTCTGCGGGG  
GCCTCTGGCGGCTGGTCTTGGCACAGCGCTGGATGGAGCGGCTCAAGACTGTGCG  
TGGGTCCAAGATGCAAGGCTTGCTGGAGCGCGTGAACACGGAGATACACTTTGTG  
20 ACCAAATGTGCCTTTCAGCCCCCCCCCAGCTGTCTTCGCTTCGTCCAGACCAACA  
TCTCCCGCCTCCTGCAGGAGACCTCCGAGCAGCTGGTGGCGCTGAAGCCCTGGAT  
CACTCGCCAGAACTTCTCCCGGTGCCTGGAGCTGCAGTGTGAGCCCGACTCCTCA  
ACCTTGGGCGGTGGGTGAGGAGGTGGGTGAGGAGGTGGATCCGGAGGTGGCACCC  
AGGACTGCTCCTTCCAACACAGCCCCATCTCCTCCGACTTCGCTGTCAAAATCCG  
25 TGAGCTGTCTGACTACCTGCTTCAA SEQ ID NO:136;

30

GCCGCCTCCAACCTGCAGGACGAGGAGCTCTGCGGGGGCCTCTGGCGGCTGGTCC  
TGGCACAGCGCTGGATGGAGCGGCTCAAGACTGTGCTGGGTCCAAGATGCAAGG  
CTTGCTGGAGCGCGTGAACACGGAGATACACTTTGTACCAAATGTGCCTTTCAG  
CCCCCCCCCAGCTGTCTTCGCTTCGTCCAGACCAACATCTCCCGCCTCCTGCAGG  
AGACCTCCGAGCAGCTGGTGGCGCTGAAGCCCTGGATCACTCGCCAGAACTTCTC  
CCGGTGCCTGGAGCTGCAGTGTGAGCCCGACTCCTCAACCCTGGGCGGTGGGTCA  
GGAGGTGGGTGAGGAGGTGGATCCGGAGGTGGCACCCAGGACTGCTCCTTCCAAC  
35 ACAGCCCCATCTCCTCCGACTTCGCTGTCAAAATCCGTGAGCTGTCTGACTACCT  
GCTTCAAGATTACCCAGTCACCGTG SEQ ID NO:137;

40

GCCGTGCTGGGTCCAAGATGCAAGGCTTGCTGGAGCGCGTGAACACGGAGATAC  
ACTTTGTACCAAATGTGCCTTTCAGCCCCCCCCCAGCTGTCTTCGCTTCGTCCA  
GACCAACATCTCCCGCCTCCTGCAGGAGACCTCCGAGCAGCTGGTGGCGCTGAAG  
CCCTGGATCACTCGCCAGAACTTCTCCCGGTGCCTGGAGCTGCAGTGTGAGCCCG  
ACTCCTCAACCCTGGGCGGTGGGTGAGGAGGTGGGTGAGGAGGTGGATCCGGAGG  
TGGCACCCAGGACTGCTCCTTCCAACACAGCCCCATCTCCTCCGACTTCGCTGTC  
45 AAAATCCGTGAGCTGTCTGACTACCTGCTTCAAGATTACCCAGTCACCGTGGCCT  
CCAACCTGCAGGACGAGGAGCTCTGCGGGGGCCTCTGGCGGCTGGTCTGGCACA  
GCGCTGGATGGAGCGGCTCAAGACT SEQ ID NO:138;

50

GCCTCCAAGATGCAAGGCTTGCTGGAGCGCGTGAACACGGAGATACACTTTGTCA  
CCAAATGTGCCTTTCAGCCCCCCCCCAGCTGTCTTCGCTTCGTCCAGACCAACAT  
CTCCCGCCTCCTGCAGGAGACCTCCGAGCAGCTGGTGGCGCTGAAGCCCTGGATC  
ACTCGCCAGAACTTCTCCCGGTGCCTGGAGCTGCAGTGTGAGCCCGACTCCTCAA  
CCCTGGGCGGTGGGTGAGGAGGTGGGTGAGGAGGTGGATCCGGAGGTGGCACCCA  
55 GGACTGCTCCTTCCAACACAGCCCCATCTCCTCCGACTTCGCTGTCAAAATCCGT  
GAGCTGTCTGACTACCTGCTTCAAGATTACCCAGTCACCGTGGCCTCCAACCTGC

AGGACGAGGAGCTCTGCGGGGGCCTCTGGCGGCTGGTCCTGGCACAGCGCTGGAT  
GGAGCGGCTCAAGACTGTCGCTGGG SEQ ID NO:139;

5 GCGCGCGCTGGTCCAGACCAACATCTCCCGCCTCCTGCAGG  
AGACCTCCGAGCAGCTGGTGGCGCTGAAGCCCTGGATCACTCGCCAGAACTTCTC  
CCGGTGCCTGGAGCTGCAGTGTGAGCCGACTCCTCAACCCTGGGCGGTGGGTCA  
GGAGGTGGGTGAGGAGGTGGATCCGGAGGTGGCACCCAGGACTGCTCCTTCCAAC  
ACAGCCCCATCTCCTCCGACTTTCGCTGTCAAAAATCCGTGAGCTGTCTGACTACCT  
10 GCTTCAAGATTACCCAGTACCCGTGGCCTCCAACCTGCAGGACGAGGAGCTCTGC  
GGGGGCCTCTGGCGGCTGGTCCTGGCACAGCGCTGGATGGAGCGGCTCAAGACTG  
TCGCTGGGTCCAAGATGCAAGGCTTGTCTGGAGCGCGTGAACACGGAGATACACTT  
TGTACCAAATGTGCCTTTCAGCCC SEQ ID NO:140;

15 GCGCGCTTCGTCCAGACCAACATCTCCCGCCTCCTGCAGGAGACCTCCGAGCAGC  
TGGTGGCGCTGAAGCCCTGGATCACTCGCCAGAACTTCTCCCGGTGCCTGGAGCT  
GCAGTGTGAGCCCGACTCCTCAACCCTGGGCGGTGGGTGAGGAGGTGGGTGAGGA  
GGTGGATCCGGAGGTGGCACCCAGGACTGCTCCTTCCAACACAGCCCCATCTCCT  
20 CCGACTTCGCTGTCAAAAATCCGTGAGCTGTCTGACTACCTGCTTCAAGATTACCC  
AGTCACCGTGGCCTCCAACCTGCAGGACGAGGAGCTCTGCGGGGGCCTCTGGCGG  
CTGGTCTCTGGCACAGCGCTGGATGGAGCGGCTCAAGACTGTCGCTGGGTCCAAGA  
TGCAAGGCTTGTCTGGAGCGCGTGAACACGGAGATACACTTTGTACCAAATGTGC  
CTTTCAGCCCCCCCCCAGCTGTCTT SEQ ID NO:142;

25 GCCACCAACATCTCCCGCCTCCTGCAGGAGACCTCCGAGCAGCTGGTGGCGCTGA  
AGCCCTGGATCACTCGCCAGAACTTCTCCCGGTGCCTGGAGCTGCAGTGTGAGCC  
CGACTCCTCAACCCTGGGCGGTGGGTGAGGAGGTGGGTGAGGAGGTGGATCCGGA  
30 GGTGGCACCCAGGACTGCTCCTTCCAACACAGCCCCATCTCCTCCGACTTCGCTG  
TCAAAAATCCGTGAGCTGTCTGACTACCTGCTTCAAGATTACCCAGTCACCGTGGC  
CTCCAACCTGCAGGACGAGGAGCTCTGCGGGGGCCTCTGGCGGCTGGTCTTGGCA  
CAGCGCTGGATGGAGCGGCTCAAGACTGTCGCTGGGTCCAAGATGCAAGGCTTGC  
TGGAGCGCGTGAACACGGAGATACACTTTGTACCAAATGTGCCTTTCAGCCCCC  
35 CCCCAGCTGTCTTCGCTTCGTCCAG SEQ ID NO:143

8. A method of producing a flt3 receptor agonist polypeptide comprising: growing under suitable nutrient conditions, a host cell transformed or transfected with  
40 a replicable vector comprising said nucleic acid molecule of claim 4, 5, 6 or 7 in a manner allowing expression of said flt3 receptor agonist polypeptide and recovering said flt3 receptor agonist polypeptide.

45 9. A composition comprising; a polypeptide of claim 1, 2, 3, or 4; and a pharmaceutically acceptable carrier.

10. A composition comprising; a polypeptide of claim 1, 2, 3, or 4; a factor selected from the group consisting of: a colony stimulating factor, a cytokine, a lymphokine, an interleukin, and a hematopoietic growth  
5 factor; and a pharmaceutically acceptable carrier.

11. The composition according to claim 10 wherein said factor is selected from the group consisting of: GM-CSF, G-CSF, c-mpl ligand, M-CSF, IL-1, IL-4, IL-2,  
10 IL-3, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-15, LIF, flt3/flk2 ligand, human growth hormone, B-cell growth factor, B-cell differentiation factor, EPO, and eosinophil differentiation factor; IL-3 variants, fusion proteins, G-CSF receptor agonists, c-  
15 mpl receptor agonists, IL-3 receptor agonists, multi-functional receptor agonists; and a pharmaceutically acceptable carrier.

12. A method of stimulating the production of  
20 hematopoietic cells in a patient, comprising the step of; administering said polypeptide of claim 1, 2, 3 or 4 to said patient.

13. A method of stimulating the production of  
25 hematopoietic cells in a patient comprising the step of; administering the composition of claim 9, 10 or 11 to said patient.

14. A method for selective ex vivo expansion of  
30 stem cells, comprising the steps of;

(a) separating hematopoietic cells from other cells;

(b) culturing said separated hematopoietic cells in a culture medium comprising; the polypeptide of  
35 claim 1, 2, 3, or 4; and

(c) harvesting said cultured cells.

15. A method for selective ex vivo expansion of hematopoietic cells, comprising the steps of;

- (a) culturing said hematopoietic cells in a  
5 culture medium, comprising; the composition of claim 9, 10 or 11; and  
(b) harvesting said cultured cells.

10 16. A method for selective ex vivo expansion of hematopoietic cells, comprising the steps of;

- (a) separating hematopoietic cells from other cells;  
(b) culturing said separated hematopoietic cells  
15 in a culture medium, comprising; the composition of claim 9, 10 or 11; and  
(c) harvesting said cultured cells.

20 17. A method for treatment of a patient having a hematopoietic disorder, comprising the steps of;

- (a) removing hematopoietic cells from said patient;  
(b) culturing said separated hematopoietic cells  
25 in a culture medium, comprising; a polypeptide of claim 1, 2, 3, or 4;  
(c) harvesting said cultured cells; and  
(d) transplanting said cultured cells into said patient.

30

18. A method for treatment of a patient having a hematopoietic disorder, comprising the steps of;

- (a) removing hematopoietic cells from said  
35 patient;  
(b) separating said hematopoietic cells from other cells;

(c) culturing said separated hematopoietic cells in a culture medium, comprising; a polypeptide of claim 1, 2, 3, or 4;

(d) harvesting said cultured cells; and

5 (e) transplanting said cultured cells into said patient.

19. A method for treatment of a patient having a hematopoietic disorder, comprising the steps of;

10 (a) removing hematopoietic cells from said patient;

(b) culturing said hematopoietic cells in a growth medium, comprising; a polypeptide of claim 1, 2, 3, or 4;

15 (c) harvesting said cultured cells; and

(d) transplanting said cultured cells into said patient.

20 20. A method for treatment of a patient having a hematopoietic disorder, comprising the steps of;

(a) removing hematopoietic cells from said patient;

25 (b) separating hematopoietic cells from other cells;

(c) culturing said separated hematopoietic cells in a growth medium, comprising; the composition of claim 9, 10 or 11;

(d) harvesting said cultured cells; and

30 (e) transplanting said cultured cells into said patient.

21. A method of human gene therapy, comprising the steps of;

35 (a) removing hematopoietic cells from a patient;

(b) culturing said hematopoietic cells in a growth medium, comprising; a polypeptide of claim 1, 2, 3, or 4;

(d) transducing said cultured cells with DNA;

5 (e) harvesting said transduced cells; and

(f) transplanting said transduced cells into said patient.

22. A method of human gene therapy, comprising  
10 the steps of;

(a) removing hematopoietic cells from a patient;

(b) separating said hematopoietic cells from other cells;

(c) culturing said separated hematopoietic cells  
15 in a growth medium, comprising; a polypeptide of claim 1, 2, 3, or 4;

(d) transducing said cultured cells with DNA;

(e) harvesting said transduced cells; and

(f) transplanting said transduced cells into said  
20 patient.

23. A method of human gene therapy, comprising the steps of;

(a) removing hematopoietic cells from a patient;

25 (b) separating said hematopoietic cells from other cells;

(c) culturing said separated hematopoietic cells in a growth medium, comprising; the composition of claim 9, 10 or 11;

30 (d) transducing said cultured cells with DNA;

(e) harvesting said transduced cells; and

(f) transplanting said transduced cells into said patient.

35

24. A method of human gene therapy, comprising the steps of;

- (a) removing hematopoietic cells from a patient;
- (b) separating said hematopoietic cells from other cells;
- (c) culturing said separated hematopoietic cells in a growth medium, comprising; the composition of claim 9, 10 or 11;
- (d) transducing said cultured cells with DNA;
- (e) harvesting said transduced cells; and
- (f) transplanting said transduced cells into said patient.

25. A method for the production of dendritic cells comprising the steps of;

15

a) separating hematopoietic progenitor cells or CD34+ cells from other cells; and

b) culturing said hematopoietic progenitor cells or CD34+ cells in a growth medium, comprising the flt-3 receptor agonists of claim 1, 2, 3 or 4.

26. The method of claim 25, further comprising the step of;

c) pulsing said culturing hematopoietic progenitor cells or CD34+ cells with an antigen.

27. The method of claim 25, wherein said growth medium, further comprises; one or more factor selected from the group consisting of; GM-CSF, IL-4, TNF- $\alpha$ , stem cell factor (SCF), flt-3 ligand, IL-3, an IL-3 variant, an IL-3 variant fusion protein, and a multi-functional receptor agonist.

28. The method of claim 26, wherein said growth medium, further comprises; one or more factor selected from the group consisting of; GM-CSF, IL-4, TNF- $\alpha$ , stem

cell factor (SCF), flt-3 ligand, IL-3, an IL-3 variant, an IL-3 variant fusion protein, and a multi-functional receptor agonist.

5           29. A method for treating a human having a tumor, infection or auto-immune disease, comprising the step of; administering the flt-3 receptor agonists of claim 1, 2, 3, or 4, to said human.

10           30. The method of claim 29, further comprising; administering one or more factor selected from the group consisting of; GM-CSF, IL-4, TNF- $\alpha$ , stem cell factor (SCF), flt-3 ligand, IL-3, an IL-3 variant, an IL-3 variant fusion protein, and a multi-functional  
15 receptor agonist.

31. The method of claim 29, further comprising the step of; administering an antigen to said patient.

20           32. The method of claim 30, further comprising the step of; administering an antigen to said patient.

33. A method for treating a human having a tumor, infection or auto-immune disease, comprising the step  
25 of;

a) mobilizing dendritic cell progenitors or mature dendritic cells by administering the flt-3 receptor agonists of claim 1, 2, 3, or 4, to said human;

30           b) removing said dendritic cell precursors or mature dendritic cells by a blood draw or pheresis;

c) pulsing said dendritic cell precursors or mature dendritic cells with an antigen; and

35           d) returning said antigen pulsed dendritic cell precursors or mature dendritic cells to said human.

34. The method of claim 33, further comprising;  
administering in step a), one or more factor selected  
from the group consisting of; GM-CSF, IL-4, TNF- $\alpha$ , stem  
5 cell factor (SCF), flt-3 ligand, IL-3, an IL-3 variant,  
an IL-3 variant fusion protein, and a multi-functional  
receptor agonist.

35. The method of claim 33, further comprising the  
10 step of; culturing said dendritic cell precursors or  
mature dendritic cells from step b), in a growth medium,  
comprising; the flt-3 receptor agonists of claim 1, 2, 3  
or 4.

36. The method of claim 34, further comprising the  
15 step of; culturing said dendritic cell precursors or  
mature dendritic cells from step b), in a growth medium,  
comprising; the flt-3 receptor agonists of claim 1, 2, 3  
or 4.

20 37. The method of claim 35, wherein said growth  
medium, further comprises one or more factor selected  
from the group consisting of; GM-CSF, IL-4, TNF- $\alpha$ , stem  
cell factor (SCF), flt-3 ligand, IL-3, an IL-3 variant,  
25 an IL-3 variant fusion protein, and a multi-functional  
receptor agonist.

38. The method of claim 36, wherein said growth  
medium, further comprises one or more factor selected  
30 from the group consisting of; GM-CSF, IL-4, TNF- $\alpha$ , stem  
cell factor (SCF), flt-3 ligand, IL-3, an IL-3 variant,  
an IL-3 variant fusion protein, and a multi-functional  
receptor agonist.

35

39. A method for treating a human having a tumor, infection or auto-immune disease, comprising the step of;

5 a) removing hematopoietic progenitor cells or CD34+ cells from said human by a blood draw or pheresis;

b) culturing said hematopoietic progenitor cells or CD34+ cells in a growth medium, comprising the flt-3 receptor agonists of claim 1, 2, 3 or 4 to produce  
10 dendritic cell precursors or mature dendritic cells;

c) returning said dendritic cell precursors or mature dendritic cells to said human.

15 40. A method for treating a human having a tumor, infection or auto-immune disease, comprising the step of;

a) removing hematopoietic progenitor cells or  
20 CD34+ cells from said patient by a blood draw or pheresis;

b) culturing said hematopoietic progenitor cells or CD34+ cells in a growth medium, comprising; the  
25 flt-3 receptor agonists of claim 1, 2, 3 or 4, to produce dendritic cell precursors or mature dendritic cells;

c) pulsing said dendritic cell precursors or  
30 mature dendritic cells with an antigen; and

d) returning said antigen pulsed dendritic cell precursors or mature dendritic cells to said human.

35 41. The method of claim 39, further comprising the step of; separating said hematopoietic progenitor cells or CD34+ cells from other cells prior to culturing.

42. The method of claim 40, further comprising the step of; separating said hematopoietic progenitor cells or CD34+ cells from other cells prior to culturing.

5

43. The method of claim 39, wherein said culture medium further comprises; one or more factor selected from the group consisting of: GM-CSF, IL-4, TNF- $\alpha$ , stem cell factor (SCF), flt-3 ligand, IL-3, an IL-3 variant,  
10 an IL-3 variant fusion protein, and a multi-functional receptor agonist.

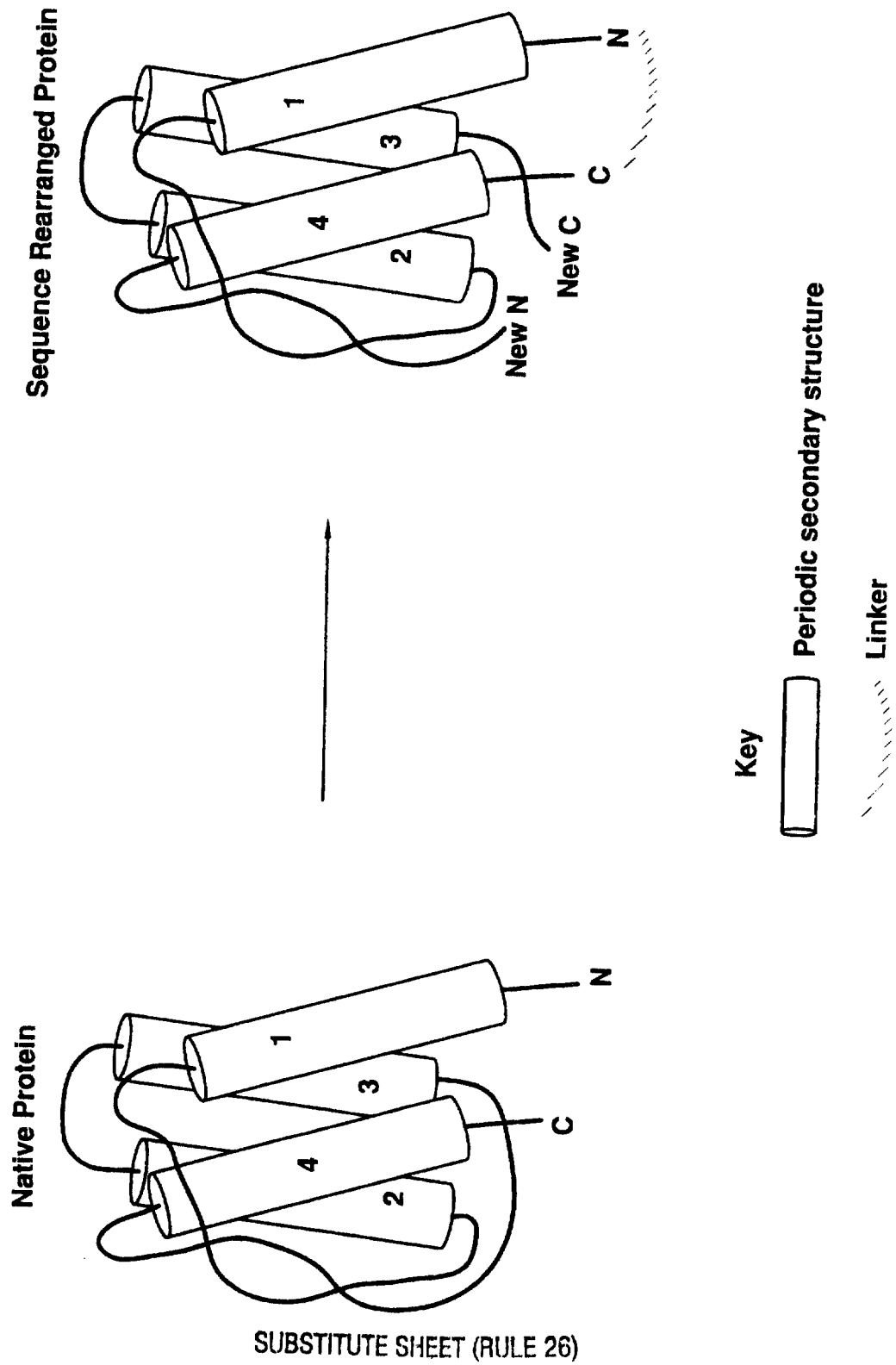
44. The method of claim 40, wherein said culture medium further comprises; one or more factor selected  
15 from the group consisting of: GM-CSF, IL-4, TNF- $\alpha$ , stem cell factor (SCF), flt-3 ligand, IL-3, an IL-3 variant, an IL-3 variant fusion protein, and a multi-functional receptor agonist.

20 45. The method of claim 41, wherein said culture medium further comprises; one or more factor selected from the group consisting of: GM-CSF, IL-4, TNF- $\alpha$ , stem cell factor (SCF), flt-3 ligand, IL-3, an IL-3 variant, an IL-3 variant fusion protein, and a multi-functional  
25 receptor agonist.

46. The method of claim 42, wherein said culture medium further comprises; one or more factor selected from the group consisting of: GM-CSF, IL-4, TNF- $\alpha$ , stem  
30 cell factor (SCF), flt-3 ligand, IL-3, an IL-3 variant, an IL-3 variant fusion protein, and a multi-functional receptor agonist.

1 / 10

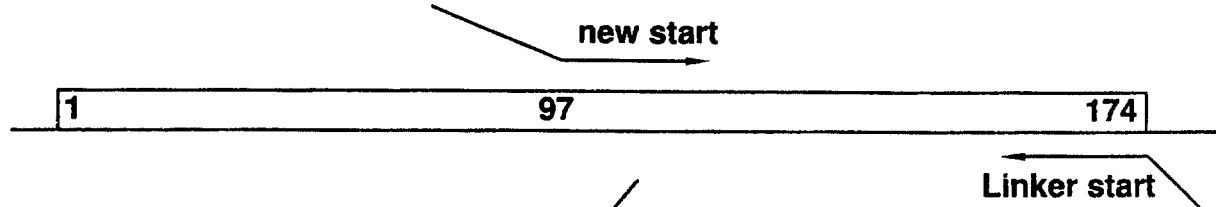
FIG.1



2 / 1 0

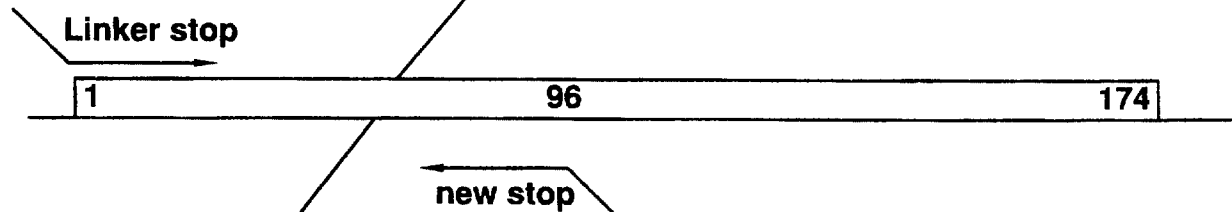
## FIG.2

first step PCR amplification



generates "Fragment Start"

second step PCR amplification



generates "Fragment Stop"

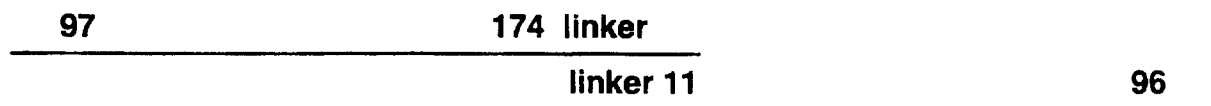
Fragment Start

Fragment Stop



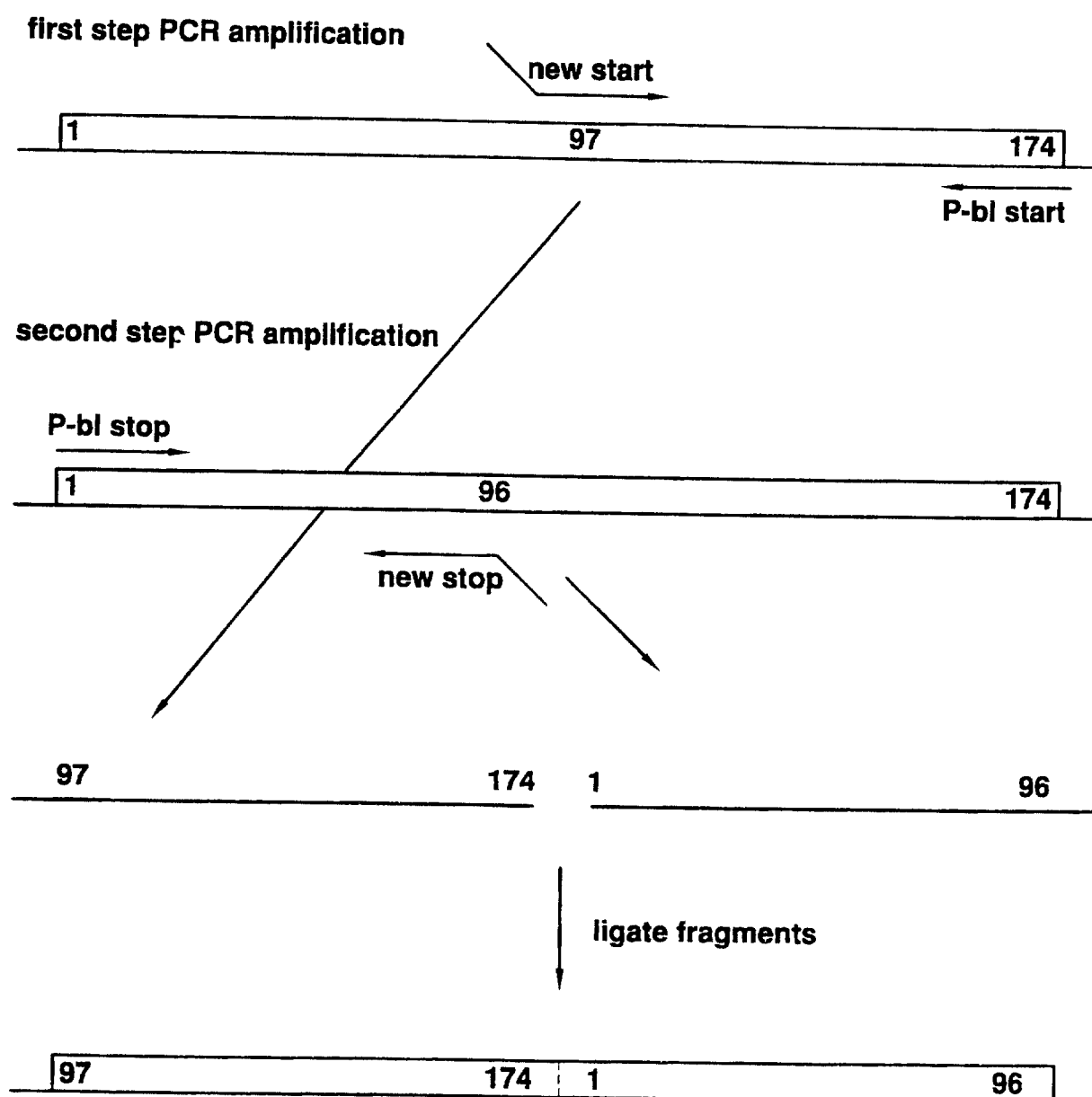
third step PCR amplification

anneal fragments

add oligos new start  
and new stop

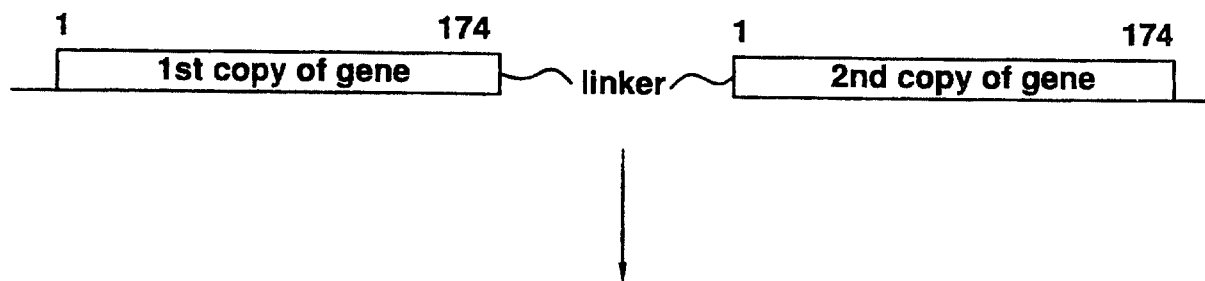
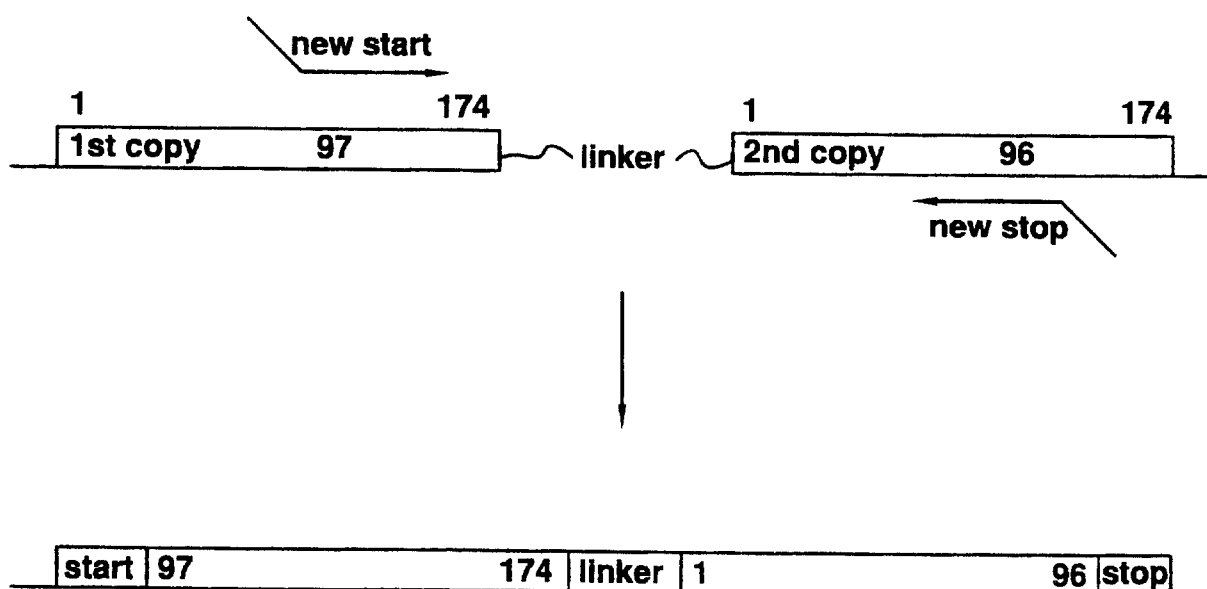
3 / 1 0

FIG.3



4 / 1 0

FIG.4

**I. Construct tandemly-duplicated template****II. PCR-amplify tandemly-duplicated template**

## FIG. 5A-1

5 / 1 0

1           ACCCAGGACTGCTCCTTCCAAACACAGCCCCATCTCCTCCGACTTCGCTGTCAAATCCCGT  
-----+-----+-----+-----+-----+-----+-----+  
60           TGGGTCCCTGACGAGGAAGTTGTGTCCGGGTAGAGGAGGCTGAAGCGACAGTTTATTAGGCA

          ThrGlnAspCysSerPheGlnHisSerProIleSerSerAspPheAlaValLysIleArg  
61           GAGCTGTCTGACTACCTGCTTCAAGATTACCCAGTCACCGTGGCCTCCAAACCTGCAGGAC  
-----+-----+-----+-----+-----+-----+-----+  
120          CTCGACAGACTGATGGACGAAGTTCTAATGGTCAGTGGCACCGGAGGTTGGACGTCCTG

          GluLeuSerAspTyrLeuLeuGlnAspTyrProValThrValAlaSerAsnLeuGlnAsp  
121          GAGGAGCTCTGCGGGGCCCTCTGGGGGCTGGTCCCTGGCACAGCGCTGGATGGAGCGGCTC  
-----+-----+-----+-----+-----+-----+-----+  
180          CTCCTCGAGACGCCCCCGGAGACCGCCGACAGGACCGTGTCCGCGACCTACCTCGCCCGAG

          GluGluLeuCysGlyGlyLeuTrpArgLeuValLeuAlaGlnArgTrpMetGluArgLeu  
181          AAGACTGTCGCTGGGTCCAAGATGCAAGGCTTCTGCTGGAGCGCGTGAACACGAGATACAC  
-----+-----+-----+-----+-----+-----+-----+  
240          TTCTGACAGCGACCCAGGTTCTACGTTCCGACCGACCTCGCGCACTTGTGCCTCTATGTG

          LysThrValAlaGlySerLysMetGlnGlyLeuLeuGluArgValAsnThrGluIleHis

## FIG. 5A-2

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```
241 TTTGTCAACCAATGTGCCTTTTCAGCCCCCCCCAGCTGTCTTCGCTTCGTCCAGACCAAC 300
-----+-----+-----+-----+-----+-----+
AAACAGTGGTTTACACGGAAGTCGGGGGGGTCGACAGAAAGCAAGCAGTCTGTG
PheValThrLysCysAlaPheGlnProProSerCysLeuArgPheValGlnThrAsn
301 ATCTCCCGCCTCCTGCAGGAGACCTCCGAGCAGCTGGTGGCGCTGAAGCCCCTGGATCACT 360
-----+-----+-----+-----+-----+-----+
TAGAGGGCGGAGGACGTCCTCTGAGGCTCGTCGACCAACCGGACTTCGGGACCTAGTGA
IleSerArgLeuLeuGlnGluThrSerGluGlnLeuValAlaLeuLysProTrpIleThr
361 CGCCAGAACTTCTCCCGGTGCCCTGGAGCTGCAGTGCAGCCCCGACTCCTCAACCCCTGCCA 420
-----+-----+-----+-----+-----+-----+
GCGGTCTTGAAGAGGGCCACGGACCTCGACGTCACAGTCGGGCTGAGGAGTTGGGACGGT
ArgGlnAsnPheSerArgCysLeuGluLeuGlnCysGlnProAspSerSerThrLeuPro
421 CCCCCATGAGTCCCCCGCCCCCTGGAGGCCACAGCCCCCGACAGCCCCCGAGCCCCCTCTG 480
-----+-----+-----+-----+-----+-----+
GGGGTACCTCAGGGGCCGGGACCTCCGGTGTCTGGGGCTGTCTGGGGCGTCTGGGGGAGAC
ProProTrpSerProArgProLeuGluAlaThrAlaProThrAlaProGlnProProLeu
```

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## FIG. 5B

```
481 CTCCTCCTACTGCTGCTGCCCGTGGCCCTCCTGCTGCTGGCCGCTGCCCTGGTGCCTGCAC
-----+-----+-----+-----+-----+-----+
540 GAGGAGGATGACGACGACGGCACCCGAGGACGACGACCGCGGACGACCCACGACGCTG
LeuLeuLeuLeuLeuProValGlyLeuLeuLeuAlaAlaTrpCysLeuHis
541 TGGCAGAGGACGGCGGAGGACACCCCGCCCTGGGAGCAGGTGCCCCCGTCCCCCAGT
-----+-----+-----+-----+-----+-----+
600 ACCGTCTCCTGCGCCGCTCCTGTGGGCGGACCCCTCGTCCACGGGGGCAGGGGTCA
TrpGlnArgThrArgArgThrProArgProGlyGluGlnValProProValProSer
601 CCCCAGGACCTGCTTGTGGAGCACTGA
-----+-----+-----+-----+-----+ 630
GGGTCTCTGGACGACGAACACCTCGTGACT
ProGlnAspLeuLeuValGluHisEnd
```

## FIG. 6A

1 ACCCAGGACTGCTCCTTCCAAACACAGCCCCATCTCCTCCGACTTCGCTGTCAAAATCCGT  
 -----+-----+-----+-----+-----+-----+  
 TGGGTCCCTGACGAGGAAGTTGTGTCGGGTAGAGGAGGCTGAAGCGACAGTTTTAGGCA 60  
  
 ThrGlnAspCysSerPheGlnHisSerProIleSerSerAspPheAlaValLysIleArg  
  
 61 GAGCTGTCTGACTACCTGCTTCAAGATTACCCAGTCAACCGTGGCCTCCAACCTGCAGGAC  
 -----+-----+-----+-----+-----+-----+  
 CTCGACAGACTGATGGACGAAGTTCTAATGGTCAAGTGCACCGGAGGTTGGACGTCCTTG 120  
  
 GluLeuSerAspTyrLeuLeuGlnAspTyrProValThrValAlaSerAsnLeuGlnAsp  
  
 121 GAGGAGCTCTGCGGGGCTCTGCGGGCTGGTCCCTGGCACAGCGCTGGATGGAGCGGCTC  
 -----+-----+-----+-----+-----+-----+  
 CTCCTCGAGACGCCCCCGGAGACCGCCGACCGACCGTGTGCGGACCTACCTCGCCGAG 180  
  
 GluGluLeuCysGlyGlyLeuTrpArgLeuValLeuAlaGlnArgTrpMetGluArgLeu  
  
 181 AAGACTGTCGCTGGGTCCAAGATGCAAGGCTTGCTGGAGCGCGGTGAACACGGAGATACAC  
 -----+-----+-----+-----+-----+-----+  
 TTCTGACAGCGACCCAGGTTCTACGTTCCGAACGACCTCGCGGCACTGTGTCCTCTATGTG 240  
  
 LysThrValAlaGlySerLysMetGlnGlyLeuLeuGluArgValAsnThrGluIleHis

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## FIG. 6B

```
241 TTTGTCACCAAAATGTGCCTTTTCAGCCCCCCCCAGCTGTCTTCGCTTCGTCCAGACCAAC
-----+-----+-----+-----+-----+-----+
AAACAGTGGTTTACACGGAAGTCGGGGGGGTCGACAGAGAAGCGAAGCAGGTCTGGTTG
-----+-----+-----+-----+-----+-----+ 300

PheValThrLysCysAlaPheGlnProProProSerCysLeuArgPheValGlnThrAsn

301 ATCTCCCGCCTCCTGCAGGAGACCTCCGAGCAGCTGGTGGCGCTGAAGCCCCTGATCACT
-----+-----+-----+-----+-----+-----+
TAGAGGGCGGAGACGTCCTCTGGAGGCTCGTCGACCACCGGACTTCGGGGACCTAGTGA
-----+-----+-----+-----+-----+-----+ 360

IleSerArgLeuLeuGlnGluThrSerGluGlnLeuValAlaLeuLysProTrpIleThr

CGCCAGAACTTCTCCCGGTGCCCTGGAGCTGCCAGTGTCAAGCCC
-----+-----+-----+-----+-----+-----+ 402
GCGGTCTTGAAGAGGGCCACGGACCCTCGACGTCACAGTCGGG

ArgGlnAsnPheSerArgCysLeuGluLeuGlnCysGlnPro
```

FIG.7

