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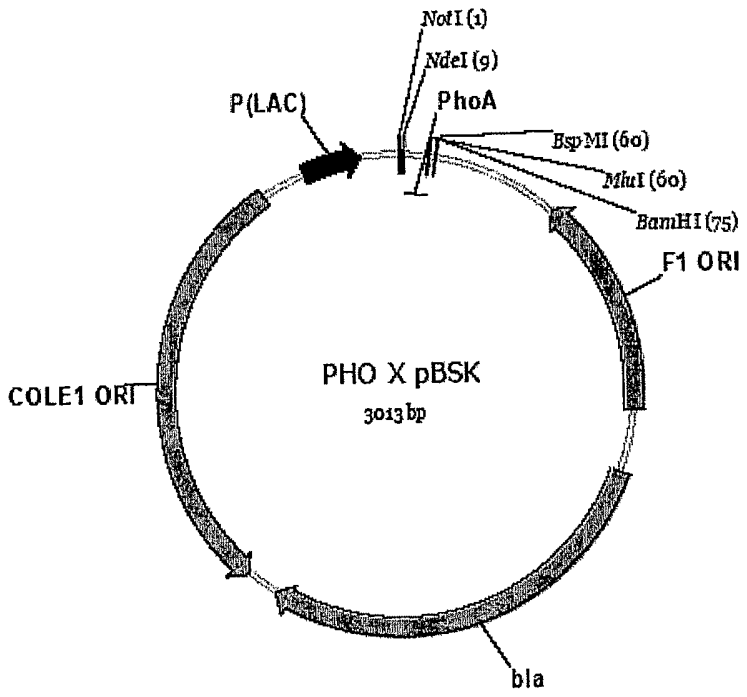

(57) Abstract: Disclosed are biologically active protein conjugates that comprise a biologically active polypeptide coupled via a peptide bond to a polypeptide comprising from 2 to about 500 units of a repeating peptide motif, wherein the biologically active protein conjugate exhibits a modified plasma half-life compared to the intrinsic half-life of the unconjugated biologically active polypeptide or protein. Also disclosed are methods of making and using the conjugated proteins, as well as methods for determining whether a given conjugate exhibits a modified half life relative to the intrinsic half life of the unconjugated polypeptide.

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BIOLOGICALLY ACTIVE PROTEINS HAVING A MODIFIED *IN VIVO* HALF-LIFE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority under 35 U.S.C 119(e) from United States Application No. 60/712,585, filed August 30, 2005 and United States Application No. 60/647,119, filed January 25, 2005, the contents of which are incorporated by reference.

TECHNICAL FIELD

[0002] This invention relates generally to biologically active proteins, and more specifically to altering the half-life of biologically active proteins.

BACKGROUND OF THE INVENTION

[0003] Biologically active proteins often have undesirable half-lives when administered as human therapeutics. Their intrinsic half-lives impose administration schedules and dosing regimens that often result in less than optimal therapeutic efficacy, compliance problems and patient inconvenience.

[0004] In the manufacture of biologically active proteins for human therapeutics, the extension of the half-life of biologically active proteins has been attempted through physical means (*e.g.*, altered route of administration, nanoparticle encapsulation and liposomal entrapment), chemical modification (*e.g.*, emulsions, pegylation and hyperglycosylation) and genetic modification (*e.g.*, modification of primary protein structure, polymer tags, human serum albumin fusion, incorporation of post-translational modification). See, for example, Lord, *et al.*, Clin. Cancer Res. 7:2085-2090 (2001), and van Der Auwera, *et al.*, Am. J. Hematol. *66*:245-251 (2001). However, such approaches have

resulted in other problems. Extension of biologically active protein half-life through physical means often introduces increased drug substance complexity with costly and time-consuming additional downstream processes during manufacturing. Chemical modification may alter the biological activity or safety profile of the biologically active protein. Where biologically active proteins are made via recombinant DNA synthesis methodology, the effect of the genetic modification on protein yield and purity in the particular cellular expression systems issues needs to be assessed for its intended use.

[0005] Accordingly, there is a need for other approaches for modifying the intrinsic half-life of biologically active proteins.

SUMMARY OF THE INVENTION

[0006] One aspect of the present invention is directed to a protein conjugate comprising a biologically active polypeptide coupled via a peptide bond to a polypeptide (amino acid extension) that comprises from 2 to about 500 repeating units of a peptide motif. The motif comprises a major constituent and a minor constituent, in which the major constituent is two or more residues of one amino acid selected from Gly (G), Asn (N) and Gln (Q), and the minor constituent is one or more residues of one amino acid selected from Ala (A), Ser (S), Thr (T), Asp (D), Gln (Q), Glu (E), His (H) and Asn (N), with the proviso that none of the amino acids is present in both the major constituent and said minor constituent, wherein the plasma half-life of the conjugate is modified relative to the intrinsic half-life of the unconjugated biologically active polypeptide. The term "modified", as used herein, refers to an increased or a decreased half-life relative to the plasma half-life of the unconjugated biologically active polypeptide or protein itself (*i.e.*, the intrinsic half life). By the phrase "intrinsic half-life" it is meant the half-life of the

native biologically active polypeptide or the half-life of the polypeptide in unconjugated form (thus including recombinant forms of the native polypeptide).

[0007] In some embodiments, the peptide motif comprises 3-6 amino acid residues (*i.e.*, 3, 4, 5 or 6). In some embodiments, wherein the peptide motif contains 5 or 6 amino acid residues, the minor constituent comprises 1 amino acid residue of said peptide. In some embodiments, the peptide motif has a sequence consisting of N and T amino acid residues, N and E amino acid residues, Q and S amino acid residues, or N and Q amino acid residues. In some embodiments, the amino acid extension is N-terminal with respect to said biologically active polypeptide; in some embodiments, it is C-terminal with respect to said biologically active polypeptide; and in other embodiments, it is situated at both the N and C-terminus with respect to said biologically active polypeptide. In some embodiments, the biologically active polypeptide is a cytokine (*e.g.*, granulocyte colony stimulating factor (G-CSF), human growth hormone, or an interferon such as a beta-interferon or a gamma-interferon), an antibody, antibody fragment, proteolytic antibody fragment or domain, single chain antibody, genetically or chemically optimized antibody or fragment thereof, a soluble gp120 or gp160 glycoprotein, a coagulation factor, a soluble receptor such as a tumor necrosis factor (TNF)-α type II receptor, a therapeutic enzyme or erythropoietin (EPO). In some embodiments, the protein conjugate has a modified half-life that is decreased relative to the intrinsic half-life of the unconjugated biologically active polypeptide, *e.g.*, wherein said biologically active polypeptide comprises a recombinant activated protein C or a recombinant Factor VII.

[0008] Another aspect of the present invention is directed to a composition comprising the protein conjugate and a carrier. In some embodiments, the composition is a

pharmaceutical composition and the carrier is a pharmaceutically acceptable carrier.

[0009] Another aspect of the present invention is directed to a chimeric DNA molecule that encodes the protein conjugate described above, as well as a vector, together comprising the chimeric DNA molecule, and a cell transformed with the chimeric DNA molecule or a vector containing it. In some embodiments, the vector is a plasmid, *e.g.*, pCE2. In some embodiments, the cell is a mammalian cell *e.g.*, a Chinese hamster ovary (CHO) cell, or a bacterium *e.g.*, *E. coli*, or yeast.

[00010] Yet another aspect of the present invention is directed to a method of making a biologically active protein conjugate comprising a biologically active polypeptide coupled via peptide bond to a polypeptide comprising from 2 to about 500 units of a peptide comprising as a major constituent, two or more residues of one amino acid selected from Gly (G), Asn (N) and Gln (Q), and as a minor constituent, one or more residues of one amino acid selected from Ala (A), Ser (S), Thr (T), Asp (D), Gln (Q), Glu (E), His (H) and Asn (N), provided that none of said amino acids is present in said major constituent and said minor constituent, such that said biologically active protein has a modified plasma half-life compared to intrinsic half-life of the unconjugated biologically active polypeptide, said method comprising: culturing a cell transformed with a chimeric DNA molecule encoding said protein conjugate under conditions whereby said DNA is expressed, thereby producing said protein conjugate; and extracting an expression product of said chimeric DNA molecule from said cell.

[00011] A further aspect of the present invention is directed to a method of determining whether a given protein conjugate exhibits a modified plasma half-life compared to the intrinsic half-life of the unconjugated biologically active polypeptide,

comprising: a) preparing a protein conjugate comprising a biologically active polypeptide coupled via a peptide bond to a polypeptide that comprises from 2 to about 500 repeating units of a peptide motif, wherein the motif comprises a major constituent and a minor constituent, in which the major constituent comprises or consists of two or more residues of one amino acid selected from the group consisting of Gly (G), Asn (N) and Gln (Q), and the minor constituent comprises or consists of one or more residues of one amino acid selected from the group consisting of Ala (A), Ser (S), Thr (T), Asp (D), Gln (Q), Glu (E), His (H) and Asn (N), wherein none of the amino acids is present in both the major constituent and said minor constituent, and b) testing the protein conjugate to determine whether the protein conjugate has a modified plasma half-life compared to the intrinsic half-life of the unconjugated biologically active polypeptide.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] Figure 1 is a schematic representation of the PHO x pBSK vector.

[0011] Figure 2 is a schematic representation of the PHO-G-CSF-NN x pBSK vector.

[0012] Figure 3 is a schematic representation of the PHO-G-CSF-(NNT)65 x pBSK vector.

[0013] Figure 4 is a schematic representation of the PHO-G-CSF-(NNT)155 x pBSK vector.

[0014] Figure 5 is a schematic representation of the PHO-G-CSF-(NNT)155 x pCE2 vector.

[0015] Figure 6 is a Western blot of several different G-CSF-polypeptide conjugates and unconjugated G-CSF.

[0016] Figure 7 is a Western blot of several different G-CSF-polypeptide conjugates and unconjugated G-CSF that were treated with PNGase F prior to electrophoresis.

[0017] Figure 8 is a Western blot of the G-CSF-(NNT)155 and G-CSF-(NNT)65 constructs (in duplicate) that were expressed in CHOK1 cells grown in PROCHO4-CDM media.

DETAILED DESCRIPTION

[0018] As used herein, the term "polypeptide" means a polymer of amino acids having no specific length, unless otherwise specified. Thus, peptides and proteins are included in the definition of "polypeptide" and these terms are used interchangeably throughout the specification, as well as in the claims. The term "polypeptide" does not exclude post-translational modifications, such as polypeptides having covalent attachment of glycosyl groups, acetyl groups, phosphate groups, lipid groups, hydroxylation of proline or lysine, and the like. Also encompassed by this definition of "polypeptide" are homologs thereof.

[0019] The term "purified" as used herein means that the biologically active protein conjugate has been purified to a level adequate for its intended use.

[0020] The present invention is directed, in a general aspect, to a protein conjugate comprising a biologically active polypeptide coupled via peptide bond to a polypeptide that comprises from 2 to about 500 units of a peptide motif that contains a major constituent of two or more residues of one amino acid selected from Gly (G), Asn (N) and Gln (Q), and a minor constituent of one or more residues of one amino acid selected from Ala (A), Ser (S), Thr (T), Asp (D), Gln (Q), Glu (E), His (H) and Asn (N), provided that none of the amino acids is present as both a major constituent and minor constituent. The protein conjugates of the present invention

have a plasma half-life greater than the corresponding unconjugated biologically active polypeptide or protein.

[0021] The repeating unit of the motif generally contains 3-7 (3, 4, 5, 6 or 7) amino acid residues. Representative peptide motifs having N (Asn) as the major constituent are described in Table 1.

[0022] Representative peptide motifs having G (Gly) as the major constituent are described in Table 2.

[0023] Representative peptide motifs having Q (Glu) as the major constituent are described in Table 3.

[0024] The number of the peptide motifs ranges from 2 to about 500. Thus, the motifs including the specific peptide motifs set forth herein, may be present in the polypeptide in the following number of units: 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257,

258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499 and 500 (thus including any subrange thereof).

[0025] As described above, the polypeptide conjugated to the biologically active polypeptide may also be referred to as an amino acid or polyamino extension (hereinafter "amino acid extension") of the biologically active polypeptide. The amino acid extension may be situated at the N-terminus, at the C-terminus or at both the N- and C-termini, with respect to the biologically active polypeptide sequence.

[0026] Without intending to be bound by theory, Applicants believe that the amino acid extensions do not adopt stable conformations and as such, do not interfere with or otherwise influence the activity of the protein. Also, limiting the amino acid extension to two different amino acids is believed to reduce the chemical complexity of the amino acid extension, which helps minimize the potential for immunogenicity, as well

as allowing for the modulation of physicochemical properties far more extensively than is possible through the use of just one type or kind of amino acid.

[0027] Broadly, the biologically active polypeptide includes any protein (including native polpeptides (*i.e.*, as they exist *in vivo*) or polypeptides produced recombinantly, such as recombinant human G-CSF (rh-G-CSF) for which a modified plasma half-life would be desirable from some standpoint, particularly from a therapeutic standpoint, meaning that when delivered to a vertebrate organism, treats, *e.g.*, cures, ameliorates, or lessens the symptoms of, a given disease in that vertebrate, or alternatively, prolongs the life of the vertebrate by slowing the progress of a terminal disease. Types of biologically active proteins include cytokines, chemokines, lymphokines, ligands, receptors, hormones, apoptosis-inducing polypeptides, enzymes, antibodies and antibody fragments, and growth factors. Examples of receptors include TNF type I receptor, IL-1 receptor type II, IL-1 receptor antagonist, IL-4 receptor and any chemically or genetically modified soluble receptors. Examples of enzymes include activated protein C, factor VII, collagenase (*e.g.*, marketed by Advance Biofactures Corporation under the name Santyl); agalsidase-beta (*e.g.*, marketed by Genzyme under the name Fabrazyme); dornase-alpha (*e.g.*, marketed by Genentech under the name Pulmozyme); alteplase (*e.g.*, marketed by Genentech under the name Activase); pegylated-asparaginase (*e.g.*, marketed by Enzon under the name Oncaspar); asparaginase (*e.g.*, marketed by Merck under the name Elspar); and imiglucerase (*e.g.*, marketed by Genzyme under the name Ceredase). Examples of specific polypeptides or proteins include, but are not limited to granulocyte macrophage colony stimulating factor (GM-CSF), granulocyte colony stimulating factor (G-CSF), macrophage colony stimulating factor (M-CSF), colony stimulating factor (CSF), interferon beta (IFN-β), interferon gamma (IFNγ), interferon gamma inducing factor I

(IGIF), transforming growth factor beta (TGF-β), RANTES (regulated upon activation, normal T-cell expressed and presumably secreted), macrophage inflammatory proteins (*e.g.*, MIP-1-α and MIP-1-β), Leishmania elongation initiating factor (LEIF), platelet derived growth factor (PDGF), tumor necrosis factor (TNF), growth factors, *e.g.*, epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), fibroblast growth factor, (FGF), nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), neurotrophin-2 (NT-2), neurotrophin-3 (NT-3), neurotrophin-4 (NT-4), neurotrophin-5 (NT-5), glial cell line-derived neurotrophic factor (GDNF), ciliary neurotrophic factor (CNTF), TNF α type II receptor, erythropoietin (EPO), insulin and soluble glycoproteins *e.g.*, gp120 and gp160 glycoproteins. The gp120 glycoprotein is a human immunodeficiency virus (HIV) envelope protein, and the gp160 glycoprotein is a known precursor to the gp120 glycoprotein.

[0028] In some embodiments, it is desirable to modify the half-life of a biologically active polypeptide such that it is decreased relative to the intrinsic half life, is desirable. Such embodiments include recombinant activated protein C (*e.g.*, marketed by Eli Lilly under the name Xigris) and recombinant Factor VII (marketed by Novo Nordisk under the name NovoSeven).

[0029] Biologically active polypeptides may be used to treat diseases such as Parkinson's disease, cancer, and heart disease. In addition, therapeutic polypeptides may be used to treat autoimmune disorders such as multiple sclerosis; Sjogren's syndrome; sarcoidosis; insulin dependent diabetes mellitus; autoimmune thyroiditis; arthritis (*e.g.*, osteoarthritis, rheumatoid arthritis, reactive arthritis, and psoriatic arthritis); ankylosing spondylitis; and scleroderma. Also, therapeutic polypeptides of the present invention can be used to treat acute and chronic inflammatory disorders, to promote increase in stature, to promote wound healing, and to

prevent rejection after transplantation of cells, tissues, or organs.

[0030] In some preferred embodiments, the polypeptide is G-CSF. G-CSF induces rapid proliferation and release of neutrophilic granulocytes to the bloodstream, thereby providing a therapeutic effect in fighting infection. As explained in U.S. Patent 6,831,158, recombinant human (rh)-G-CSF is generally used for treating various forms of leukopenia (a reduced level of white blood cells) and neutropenia (a reduced level of neutrophils). Leukopenia and neutropenia result in an increased susceptibility to various infections.

[0031] Commercial preparations of rh-G-CSF are available under the names filgrastim (GRAN® and NEUPOGEN®), lenograstim (NEUTROGIN® and GRANOCYTE®) and nartograstim (NEU-UP®). GRAN® and NEUPOGEN® are non-glycosylated and produced in recombinant *E. coli* cells. NEUTROGIN® and GRANOCYTE® are glycosylated and produced in recombinant CHO cells. NEU-UP® is non-glycosylated with five amino acids substituted at the N-terminal region of intact rh-G-CSF produced in recombinant *E. coli* cells.

[0032] Aside from G-CSF, *per se*, G-CSF analogs that are biologically functional or have biological activity are also useful. Methods of preparing rh-G-CSF are disclosed in U.S. Patent 4,810,643. Various G-CSF analogs are also reported in U.S. Patent 4,810,643. The polynucleotide encoding rh-G-CSF and the amino acid structure of rh-G-CSF are both provided in U.S. Patent 5,985,265.

[0033] A representative example of an amino acid sequence (and the corresponding polynucleotide sequence) of a protein conjugate of the present invention is shown in Table 4. The PHO leader sequence is included.

[0034] In the amino acid sequence, the PHO leader sequence is from amino acids 1 to 18, G-CSF is from amino acids 19 to 192,

and the NNT_{155} amino acid extension is from amino acids 193 to 347. The stop codon is denoted by the "*" symbol.

[0035] As depicted in the polynucleotide sequence, nucleic acids 1 to 54 encode the PHO leader sequence, nucleic acids 55 to 576 encode G-CSF, and nucleic acids 577 to 1041 encode the NNT_{155} amino acid extension. Nucleic acids 1042 to 1044 (TAG) constitute the stop codon.

[0036] In some embodiments, the number of repeating peptide units is between 75 and 225. Thus, in the case of a protein conjugate containing G-CSF linked to a polypeptide containing repeating units of peptide motif having the sequence NNT, embodiments of the present invention may include any of the following protein conjugates: G-CSF-$(NNT)_{75}$, G-CSF-$(NNT)_{76}$, G-CSF-$(NNT)_{77}$, G-CSF-$(NNT)_{78}$, G-CSF-$(NNT)_{79}$, G-CSF-$(NNT)_{80}$, G-CSF-$(NNT)_{81}$, G-CSF-$(NNT)_{82}$, G-CSF-$(NNT)_{83}$, G-CSF-$(NNT)_{84}$, G-CSF-$(NNT)_{85}$, G-CSF-$(NNT)_{86}$, G-CSF-$(NNT)_{87}$, G-CSF-$(NNT)_{88}$, G-CSF-$(NNT)_{89}$, G-CSF-$(NNT)_{90}$, G-CSF-$(NNT)_{91}$, G-CSF-$(NNT)_{92}$, G-CSF-$(NNT)_{93}$, G-CSF-$(NNT)_{94}$, G-CSF-$(NNT)_{95}$, G-CSF-$(NNT)_{96}$, G-CSF-$(NNT)_{97}$, G-CSF-$(NNT)_{98}$, G-CSF-$(NNT)_{99}$, G-CSF-$(NNT)_{100}$, G-CSF-$(NNT)_{101}$, G-CSF-$(NNT)_{102}$, G-CSF-$(NNT)_{103}$, G-CSF-$(NNT)_{104}$, G-CSF-$(NNT)_{105}$, G-CSF-$(NNT)_{106}$, G-CSF-$(NNT)_{107}$, G-CSF-$(NNT)_{108}$, G-CSF-$(NNT)_{109}$, G-CSF-$(NNT)_{110}$, G-CSF-$(NNT)_{111}$, G-CSF-$(NNT)_{112}$, G-CSF-$(NNT)_{113}$, G-CSF-$(NNT)_{114}$, G-CSF-$(NNT)_{115}$, G-CSF-$(NNT)_{116}$, G-CSF-$(NNT)_{117}$, G-CSF-$(NNT)_{118}$, G-CSF-$(NNT)_{119}$, G-CSF-$(NNT)_{120}$, G-CSF-$(NNT)_{121}$, G-CSF-$(NNT)_{122}$, G-CSF-$(NNT)_{123}$, G-CSF-$(NNT)_{124}$, G-CSF-$(NNT)_{125}$, G-CSF-$(NNT)_{126}$, G-CSF-$(NNT)_{127}$, G-CSF-$(NNT)_{128}$, G-CSF-$(NNT)_{129}$, G-CSF-$(NNT)_{130}$, G-CSF-$(NNT)_{131}$, G-CSF-$(NNT)_{132}$, G-CSF-$(NNT)_{133}$, G-CSF-$(NNT)_{134}$, G-CSF-$(NNT)_{135}$, G-CSF-$(NNT)_{136}$, G-CSF-$(NNT)_{137}$, G-CSF-$(NNT)_{138}$, G-CSF-$(NNT)_{139}$, G-CSF-$(NNT)_{140}$, G-CSF-$(NNT)_{141}$, G-CSF-$(NNT)_{142}$, G-CSF-$(NNT)_{143}$, G-CSF-$(NNT)_{144}$, G-CSF-$(NNT)_{145}$, G-CSF-$(NNT)_{146}$, G-CSF-$(NNT)_{147}$, G-CSF-$(NNT)_{148}$, G-CSF-$(NNT)_{149}$, G-CSF-$(NNT)_{150}$, G-CSF-$(NNT)_{151}$, G-CSF-$(NNT)_{152}$, G-CSF-$(NNT)_{153}$, G-CSF-$(NNT)_{154}$, G-CSF-$(NNT)_{155}$, G-CSF-$(NNT)_{156}$, G-CSF-$(NNT)_{157}$, G-CSF-$(NNT)_{158}$, G-CSF-$(NNT)_{159}$, G-CSF-$(NNT)_{160}$, G-CSF-$(NNT)_{161}$, G-CSF-$(NNT)_{162}$, G-CSF-$(NNT)_{163}$, G-CSF-$(NNT)_{164}$, G-CSF-

$(NNT)_{165}$, G-CSF-$(NNT)_{166}$, G-CSF-$(NNT)_{167}$, G-CSF-$(NNT)_{168}$, G-CSF-$(NNT)_{169}$, G-CSF-$(NNT)_{170}$, G-CSF-$(NNT)_{171}$, G-CSF-$(NNT)_{172}$, G-CSF-$(NNT)_{173}$, G-CSF-$(NNT)_{174}$, G-CSF-$(NNT)_{175}$, G-CSF-$(NNT)_{176}$, G-CSF-$(NNT)_{177}$, G-CSF-$(NNT)_{178}$, G-CSF-$(NNT)_{179}$, G-CSF-$(NNT)_{180}$, G-CSF-$(NNT)_{181}$, G-CSF-$(NNT)_{182}$, G-CSF-$(NNT)_{183}$, G-CSF-$(NNT)_{184}$, G-CSF-$(NNT)_{185}$, G-CSF-$(NNT)_{186}$, G-CSF-$(NNT)_{187}$, G-CSF-$(NNT)_{188}$, G-CSF-$(NNT)_{189}$, G-CSF-$(NNT)_{190}$, G-CSF-$(NNT)_{191}$, G-CSF-$(NNT)_{192}$, G-CSF-$(NNT)_{193}$, G-CSF-$(NNT)_{194}$, G-CSF-$(NNT)_{195}$, G-CSF-$(NNT)_{196}$, G-CSF-$(NNT)_{197}$, G-CSF-$(NNT)_{198}$, G-CSF-$(NNT)_{199}$, G-CSF-$(NNT)_{200}$, G-CSF-$(NNT)_{201}$, G-CSF-$(NNT)_{202}$, G-CSF-$(NNT)_{203}$, G-CSF-$(NNT)_{204}$, G-CSF-$(NNT)_{205}$, G-CSF-$(NNT)_{206}$, G-CSF-$(NNT)_{207}$, G-CSF-$(NNT)_{208}$, G-CSF-$(NNT)_{209}$, G-CSF-$(NNT)_{210}$, G-CSF-$(NNT)_{211}$, G-CSF-$(NNT)_{212}$, G-CSF-$(NNT)_{213}$, G-CSF-$(NNT)_{214}$, G-CSF-$(NNT)_{215}$, G-CSF-$(NNT)_{216}$, G-CSF-$(NNT)_{217}$, G-CSF-$(NNT)_{218}$, G-CSF-$(NNT)_{219}$, G-CSF-$(NNT)_{220}$, G-CSF-$(NNT)_{221}$, G-CSF-$(NNT)_{222}$, G-CSF-$(NNT)_{223}$, G-CSF-$(NNT)_{224}$ and G-CSF-$(NNT)_{225}$

[0037] In other preferred embodiments, the polypeptide is EPO. As explained in Krantz, Blood 77:419 (1991), naturally occurring EPO stimulates the division and differentiation of committed erythoid progenitors in the bone marrow and exerts its biological activity by binding to receptors and erythroid precursors. EPO has been manufactured biosynthetically using recombinant technology as the product of a cloned human EPO (hEPO) gene inserted into and expressed in Chinese hamster ovary (CHO) cells. See Egrie, *et al.*, Immunobiol. 72:213-224 (1986). The primary structure (*i.e.*, amino acid sequence) of the predominant, fully processed form of hEPO is illustrated in U.S. Patent 6,583,272. In EPO, there are two disulfide bridges between Cys^{7} - Cys^{161} and Cys^{29} - Cys^{33}. The molecular weight of the polypeptide chain of EPO without the sugar moieties is 18,236 DA. In the intact EPO molecule, approximately 40% of the molecular weight is accounted for by carbohydrate groups that glycosylate the protein at glycosylation sites on the protein. See Sasaki, *et al.*, J. Biol. Chem. *262*:12059 (1987).

[0038] Because hEPO is essential in red blood formation, the hormone is useful in the treatment of blood disorders characterized by low or defective red blood cell production. Clinically, EPO is used in the treatment of anemia in chronic renal failure (CRF) patients. See Eschbach, *et al.*, NEJM *316*:73-78 (1987); Eschbach, *et al.*, Ann. Intern. Med. *111*:992 (1989); Egrie, *et al.*, Kidney Intl. *33*:262 (1988); and Lim *et al.*, Ann. Intern. Med. *110*:108-114 (1989). EPO has also been used for the treatment of anemia in Acquired Immune Deficiency Syndrome (AIDS) and cancer patients undergoing chemotherapy. See R.P. Danna, *et al.*, Erythropoietin In Clinical Applications - An International Perspective 301-324 (M.B. Garnick, ed., Marcel Dekker 1990).

[0039] Amino acid and corresponding nucleotide sequences of EPO, as well as other biologically active polypeptides useful in the present invention, are set forth in Table 5. Two other amino acid sequences of EPO are set forth in Table 6.

[0040] The protein conjugate may further comprise one or more affinity tags. Generally, an affinity tag is a polypeptide segment that facilitates isolation, purification or detection of the fusion protein containing the affinity tag. In principle, any peptide or protein for which an antibody or other specific binding agent is available can be used as an affinity tag. Representative affinity tags include a poly-histidine tract, protein A (Nilsson, *et al.*, EMBO J. *4*:1075, (1985); Nilsson, *et al.*, Methods Enzymol. *198*:3, (1991)), glutathione S transferase (Smith *et al.*, Gene *67*:31 (1988)), maltose binding protein (Kellerman *et al.*, Methods Enzymol. *90*:459-463 (1982); Guan, *et al.*, Gene *67*:21-30 (1987)), Glu-Glu affinity tag (Grussenmeyer, *et al.*, Proc. Natl. Acad. Sci. USA *82*:7952-4 (1985); see oNDEPHO-1R), substance P, Flag™ peptide (Hopp, *et al.*, Biotechnology *6*:1204-10 (1988)), streptavidin binding peptide, thioredoxin, ubiquitin, cellulose binding protein, T7 polymerase, or other antigenic

epitope or binding domain. See, in general, Ford, *et al.*, Protein Expression and Purification *2*:95-107 (1991). DNAs encoding affinity tags are available from commercial suppliers (*e.g.*, Pharmacia Biotech, Piscataway, New Jersey; New England Biolabs, Beverly, Massachusetts; and Eastman Kodak, New Haven, Connecticut).

[0041] As in the case of the amino acid extension, the affinity tag may be situated at the N-terminal, C-terminal, or both N-terminal and C-terminal with respect to the biologically active polypeptide sequence.

[0042] The present invention is also directed to a method of making the protein conjugates. The method involves culturing a cell transformed with a chimeric DNA molecule encoding the protein conjugate under conditions whereby the DNA is expressed, thereby producing the protein conjugate; and extracting an expression product of the chimeric DNA molecule from the cell or culture medium (or a milleau from the cell culture). In contrast to protein conjugates formed by chemical means (*e.g.*, the commercial product NEULASTA (PEG-G-CSF, which is a covalent conjugate of recombinant methionyl human G-CSF and monomethionyl polyethylene glycol), the conjugation in the present invention is performed recombinantly as opposed to through physical or chemical means, resulting in the production of the biologically active protein and the polypeptide as components of a continuous protein. A linker, *e.g.*, about 10-20 amino acids in length, may be used to join the protein with the amino acid extension.

[0043] The chimeric DNA molecule includes a gene or polynucleotide fragment that encodes a protein portion and one or more gene fragments *e.g.*, oligonucleotides that together encode the polypeptide or amino acid extension. Oligonucleotides encoding the peptide motifs contained in the amino acid extension (and which encode the peptide motifs specifically disclosed herein) are set forth in Table 7. (The

one-letter symbols used in Table 7 are explained in Table 8.) The DNA molecules may further contain fragments that encode affinity tags, linkers, as well as 5′ and 3′ regulatory elements. The gene or polynucleotide that encodes a protein portion may be any gene or polynucleotide known to encode the desired protein or polypeptide of the protein portion. Such genes and polynucleotides, and the primers used to generate them, are protein or polypeptide specific and well known in the art. The ligated oligonucleotides encoding the polypeptide portion may be produced according to procedures set forth above and described in Example 1. The oligonucleotides may be of any length, but are preferably designed to avoid the use of repetitive DNA sequences that are known to inhibit transcription. For instance, ligated oligonucleotides containing combinations of two glutamate codons are less likely to adopt a structural configuration that impedes gene expression than a polynucleotide made up of only one glutamate codon. The chimeric DNA molecule encoding the protein conjugate of the present invention may be engineered to contain codons encoding methionine (M) and/or proline (P) amino acid at its 5′ end to facilitate expression.

[0044] The conjugates of the present invention are made via standard recombinant techniques in molecular biology. In some embodiments, a gene or polynucleotide encoding the biologically active protein is first cloned into a construct, *e.g.*, a plasmid or other vector. Then, the oligonuleotides that encode the repeating units of the polypeptide portion are cloned into the construct through a ligation or multimerization scheme, in which the oligonucleotides are ligated together to form a polynucleotide that encodes the polypeptide portion. In this manner, the oligonucleotides are added to the gene or polynucleotide that encodes the protein portion, thereby producing the chimeric DNA molecule within the construct. As an option, the chimeric DNA molecule may be transferred or cloned into another construct that is a more

appropriate expression vector. At this point, a host cell capable of expressing the chimeric DNA molecule is transformed with the chimeric DNA molecule. The transformation may occur with or without the utilization of a carrier, such as an expression vector. Then, the transformed host cell is cultured under conditions suitable for expression of the chimeric DNA molecule, resulting in the encoding of the protein conjugate.

[0045] Methods of ligation or multimerization useful in the present invention are well known. *See*, Joseph Sambrook, *et al.*, Molecular Cloning: A Laboratory Manual, 2nd ed., 1.53 (Cold Spring Harbor Laboratory Press 1989).

[0046] The cloning process may take place through "directional cloning", which is well known in the art. Directional cloning refers to the insertion of a polynucleotide into a plasmid or vector in a specific and predefined orientation. Once cloned into a vector, a polynucleotide sequence can be lengthened at its 3′ end or other polynucleotides inserted at its 5′ and/or 3′ ends. Such a design provides an efficient and relatively easy way to create large polymers without having to perform multiple rounds of ligation. The vector preferably contains restriction sites upstream of a cloned polynucleotide, but downstream of regulatory elements required for expression to facilitate the insertion of the second polynucleotide.

[0047] To facilitate directional cloning, "adapter oligonucleotides" may be ligated to the 5′ and 3′ ends of the chimeric DNA molecule encoding the protein conjugate. Preferably, the adapters contain restriction sites that are compatible with those present in the expression vector. The 3′ adapter oligonucleotide may also comprise a stop codon to designate the end of the encoding sequence to which it is ligated. The oligonucleotides encoding the polypeptide portion are preferably added in excess of the adapter

oligonucleotides to increase the likelihood that a long polynucleotide is generated after ligation.

[0048] The methodology is not limited to any particular cloning strategy. The skilled artisan may use any variety of cloning strategies to produce a construct that comprises a chimeric DNA molecule of the present invention.

[0049] The chimeric DNA molecule can be introduced into the host cells in accordance with known techniques well known to those skilled in the art. These techniques include, but are not limited to, transformation using calcium phosphate co-precipitated chimeric DNA molecules, lipidic reagent co-transfection (*i.e.*, Lipofectamine), electroporation, transduction by contacting the cells with a virus, or microinjection of the chimeric DNA molecules into the cells. The host cell can be a higher eukaryotic cell, such as a mammalian cell, or a lower eukaryotic cell, such as a yeast cell, or the host cell can be a prokaryotic cell, such as a bacterial cell. Suitable prokaryotic hosts for transformation include *E. coli*, *Bacillus subtilis*, *Salmonella typhimurium* and various species within the genera *Pseudomonas*, *Streptomyces*, and *Staphylococcus*, although others may also be employed as a matter of choice.

[0050] A wide variety of host/expression vector combinations are employed in expressing the protein conjugates of the present invention. Generally, recombinant expression vectors will include origins of replication and selectable markers permitting transformation of the host cell (*e.g.*, dihydrofolate reductase or neomycin resistance for eukaryotic cell culture, or such as tetracycline or ampicillin resistance in *E. coli*, or the *S. cerevisiae TRP*1 gene), and a promoter derived from a highly-expressed gene to direct transcription of a downstream structural sequence. Such promoters can be derived from operons encoding glycolytic enzymes such as 3-phosphoglycerate kinase (PGK), A-factor, acid phosphatase, or

heat shock proteins, among others. The heterologous structural sequence is assembled in appropriate phase with translation initiation and termination sequences, and in some embodiments, a leader sequence capable of directing secretion of translated protein conjugate. The vector will further comprise an origin of replication to ensure maintenance of the vector and to, if desirable, provide amplification within the host.

[0051] Useful expression vectors that can be used include, for example, segments of chromosomal, non-chromosomal and synthetic DNA sequences. Suitable vectors include, but are not limited to, derivatives of SV40 and pcDNA and known bacterial plasmids such as col EI, pCR1, pBR322, pMal-C2, pET, pGEX as described by Smith, *et al.*, Gene *67*:31-40 (1988), pMB9 and derivatives thereof, plasmids such as RP4, phage DNAs such as the numerous derivatives of phage I such as NM989, as well as other phage DNA such as M13 and filamentous single stranded phage DNA; yeast plasmids such as the 2 micron plasmid or derivatives of the 2m plasmid, as well as centomeric and integrative yeast shuttle vectors; vectors useful in eukaryotic cells such as vectors useful in insect or mammalian cells; vectors derived from combinations of plasmids and phage DNAs, such as plasmids that have been modified to employ phage DNA or the expression control sequences; and the like. The requirements are that the vectors are replicable and viable in the host cell of choice. Low- or high-copy number vectors may be used as desired.

[0052] For example in a baculovirus expression system, both non-fusion transfer vectors, such as, but not limited to pVL941 (*BamHI* cloning site, available from Summers, *et al.*, Virology *84*:390-402 (1978)), pVL1393 (*BamHI*, *Sma*I, *Xba*I, *EcoR*I, *Not*I, *Xma*III, *Bgl*II and *Pst*I cloning sites; Invitrogen), pVL1392 (*Bgl*II, *Pst*I, *Not*I, *Xma*III, *EcoR*I, *Xba*II, *Sma*I and *BamHI* cloning site; Summers, *et al.*, Virology *84*:390-402 (1978) and Invitrogen) and pBlue*Bac*III (*BamHI*, *Bgl*II,

*Pst*I, *Nco*I and *Hind*III cloning site, with blue/white recombinant screening, Invitrogen), and fusion transfer vectors such as, but not limited to, pAc700 (*BamH*I and *Kpn*I cloning sites, in which the *Bam*HI recognition site begins with the initiation codon; Summers, *et al.*, Virology *84*:390-402 (1978)), pAc701 and pAc70-2 (same as pAc700, with different reading frames), pAc360 (*BamH*I cloning site 36 base pairs downstream of a polyhedrin initiation codon; Invitrogen (1995)) and pBlueBacHisA, B, C (three different reading frames with *BamH*I, *Bgl*II, *Pst*I, *Nco*I and *Hind*III cloning site, an N-terminal peptide for ProBond purification and blue/white recombinant screening of plaques; Invitrogen (220) can be used.

[0053] Mammalian expression vectors will comprise an origin of replication, a suitable promoter and enhancer, and also any necessary ribosome binding sites, polyadenylation site, splice donor and acceptor sites, transcriptional termination sequences, and 5' flanking nontranscribed sequences. DNA sequences derived from the SV40 splice, and polyadenylation sites may be used to provide the required nontranscribed genetic elements. Mammalian expression vectors contemplated for use in the invention include vectors with inducible promoters, such as the dihydrofolate reductase promoters, any expression vector with a DHFR expression cassette or a DHFR/methotrexate co-amplification vector such as pED (*Pst*I, *Sal*I, *Sba*I, *Sma*I and *EcoR*I cloning sites, with the vector expressing both the cloned gene and DHFR; Randal J. Kaufman, 1991, Randal J. Kaufman, Current Protocols in Molecular Biology, 16,12 (1991)). Alternatively a glutamine synthetase/methionine sulfoximine co-amplification vector, such as pEE14 (*Hind*III, *Xba*I, *Sma*I, *Sba*I, *EcoR*I and *Bcl*I cloning sites in which the vector expresses glutamine synthetase and the cloned gene; Celltech). A vector that directs episomal expression under the control of the Epstein Barr Virus (EBV) or nuclear antigen (EBNA) can be used such as

pREP4 (*BamHI*, *SfiI*, *XhoI*, *NotI*, *NheI*, *HindIII*, *NheI*, *PvuII* and *KpnI* cloning sites, constitutive RSV-LTR promoter, hygromycin selectable marker; Invitrogen), pCEP4 (*BamHI*, *SfiI*, *XhoI*, *NotI*, *NheI*, *HindIII*, *NheI*, *PvuII* and *KpnI* cloning sites, constitutive hCMV immediate early gene promoter, hygromycin selectable marker; Invitrogen), pMEP4 (*KpnI*, *PvuI*, *NheI*, *HindIII*, *NotI*, *XhoI*, *SfiI*, *BamHI* cloning sites, inducible methallothionein IIa gene promoter, hygromycin selectable marker, Invitrogen), pREP8 (*BamHI*, *XhoI*, *NotI*, *HindIII*, *NheI* and *KpnI* cloning sites, RSV-LTR promoter, histidinol selectable marker; Invitrogen), pREP9 (*KpnI*, *NheI*, *HindIII*, *NotI*, *XhoI*, *SfiI*, *BamHI* cloning sites, RSV-LTR promoter, G418 selectable marker; Invitrogen), and pEBVHis (RSV-LTR promoter, hygromycin selectable marker, N-terminal peptide purifiable via ProBond resin and cleaved by enterokinase; Invitrogen).

[0054] Selectable mammalian expression vectors for use in the invention include, but are not limited to, pRc/CMV (*HindIII*, *BstXI*, *NotI*, *SbaI* and *ApaI* cloning sites, G418 selection, Invitrogen), pRc/RSV (*HindII*, *SpeI*, *BstXI*, *NotI*, *XbaI* cloning sites, G418 selection, Invitrogen) and the like. Vaccinia virus mammalian expression vectors (see, for example, Randall J. Kaufman, Current Protocols in Molecular Biology 16.12 (Frederick M. Ausubel, *et al.*, eds. Wiley 1991) that can be used in the present invention include, but are not limited to, pSC11 (*SmaI* cloning site, TK- and β-gal selection), pMJ601 (*SalI*, *SmaI*, *AflI*, *NarI*, *BspMII*, *BamHI*, *ApaI*, *NheI*, *SacII*, *KpnI* and *HindIII* cloning sites; TK- and β-*gal* selection), pTKgptF1S (*EcoRI*, *PstI*, *SalII*, *AccI*, *HindII*, *SbaI*, *BamHI* and *Hpa* cloning sites, TK or XPRT selection) and the like.

[0055] Yeast expression systems that can also be used in the present include, but are not limited to, the non-fusion pYES2 vector (*XbaI*, *SphI*, *ShoI*, *NotI*, *GstXI*, *EcoRI*, *BstXI*, *BamHI*, *SacI*, *KpnI* and *HindIII* cloning sites, Invitrogen), the fusion pYESHisA, B, C (*XbalI*, *SphI*, *ShoI*, *NotI*, *BstXI*, *EcoRI*, *BamHI*,

*Sac*I, *Kpn*I and *Hind*III cloning sites, N-terminal peptide purified with ProBond resin and cleaved with enterokinase; Invitrogen), pRS vectors and the like.

[0056] One particularly preferred vector for use in the present invention is the plasmid pCE2. The pCE2 plasmid may be obtained by any method known in the art. One such method, which was utilized in Example 2.A., is described in Leung, *et al.*, Proc. Natl. Acad. Sci. USA *92*:4813-4817 (1995).

[0057] In a preferred embodiment, the chimeric DNA molecules can be inserted into an expression vector that already contains the necessary elements for the transcription and translation of the inserted chimeric DNA molecule.

[0058] In addition, the expression vector containing the chimeric DNA molecule may include drug selection markers. Such markers aid in cloning and in the selection or identification of vectors containing chimeric DNA molecules. For example, genes that confer resistance to neomycin, puromycin, hygromycin, dihydrofolate reductase (DHFR), guanine phosphoribosyl transferase (GPT), zeocin, and histidinol are useful selectable markers. Alternatively, enzymes such as herpes simplex virus thymidine kinase (tk) or chloramphenicol acetyltransferase (CAT) may be employed. Immunologic markers also can be employed. Any known selectable marker may be employed so long as it is capable of being expressed simultaneously with the nucleic acid encoding a gene product. Further examples of selectable markers are well known to one of skill in the art and include reporters such as enhanced green fluorescent protein (EGFP), beta-galactosidase (β-gal) or chloramphenicol acetyltransferase (CAT).

[0059] Consequently, mammalian and typically human cells, as well as bacterial, yeast, fungi, insect, nematode and plant cells can used in the present invention as host cells and may be transformed by the expression vector as defined herein. In

some cellular hosts, such as mammalian cells, the cell containing the chimeric DNA molecule may be "isolated" in that it is removed from its original environment (*e.g.*, the natural environment if it is naturally occurring). In other embodiments, such as plants, the cells do not have to be isolated in that the whole plant may be used rather than a culture of plant cells or parts.

[0060] Examples of suitable cells include, but are not limited to, VERO cells, HELA cells such as ATCC No. CCL2, CHO cell lines such as ATCC No. CCL61, COS cells such as COS-7 cells and ATCC No. CRL 1650 cells, W138, BHK, HepG2, 3T3 such as ATCC No. CRL6361, A549, PC12, K562 cells, 293 cells, Sf9 cells such as ATCC No. CRL1711 and Cv1 cells such as ATCC No. CCL70.

[0061] Other suitable cells that can be used in the present invention include, but are not limited to, prokaryotic host cells strains such as *Escherichia coli,* (*e.g.*, strain DH5-α), *Bacillus subtilis*, *Salmonella typhimurium*, or strains of the genera of *Pseudomonas*, *Streptomyces* and *Staphylococcus*. Further suitable cells that can be used in the present invention include yeast cells such as those of *Saccharomyces* such as *Saccharomyces cerevisiae*.

[0062] Host cells containing the polynucleotides of interest can be cultured in conventional nutrient media (*e.g.*, Ham's nutrient mixture) modified as appropriate for activating promoters, selecting transformants or amplifying genes. The culture conditions, such as temperature, pH and the like, are those previously used with the host cell selected for expression, and will be apparent to the ordinarily skilled artisan. Cells are typically harvested by centrifugation, disrupted by physical or chemical means, and the resulting crude extract retained for further purification. Microbial cells employed in expression of proteins can be disrupted by any convenient method, including freeze-thaw cycling, sonication, mechanical disruption, or use of cell lysing

agents, all of which are well known to those skilled in the art. Embodiments that involve cell lysis may entail use of a buffer that contains protease inhibitors that limit degradation after expression of the chimeric DNA molecule. Suitable protease inhibitors include leupeptin, pepstatin or aprotinin. The supernatant then may be precipitated in successively increasing concentrations of saturated ammonium sulfate.

[0063] The protein conjugates product may be purified via one or more techniques. Typically, purification entails combinations of individual procedures such as gel filtration, affinity purification, salt fractionation, ion exchange chromatography, size exclusion chromatography, hydroxylapatite adsorption chromatography, hydrophobic interaction chromatography and gel electrophoresis. Protein refolding steps can be used, as necessary, in completing configuration of the protein conjugate. High performance liquid chromatography (HPLC) is often useful for final purification steps. See, in general, Robert K. Scopes, Protein Purification: Principles and Practice (Charles R. Castor, ed., Springer-Verlag 1994) and Joseph Sambrook, Molecular Cloning: A Laboratory Manual, 2nd edition (Cold Spring Harbor Laboratory Press 1989). Examples of multi-step purification separations are also described in Baron, *et al.*, Crit. Rev. Biotechnol. *10*:179-90 (1990) and Below, *et al.*, J. Chromatogr. A. *679*:67-83 (1994).

[0064] The conjugates are tested prior to use to determine whether they exhibit modified plasma half-life compared to the unconjugated protein. For example, in experiments conducted with G-CSF and various amino acid extensions such as (NNT), Applicants found that the half-life was increased in one case, and in other cases, was decreased. The tests may be conducted in accordance with standard techniques in pharmacokinetics, as shown in example 3. This procedure entails administration of a predetermined dose of the conjugate to an animal, preferably

a laboratory animal such as a rodent, *e.g.*, mouse, collect plasma from the animal at predetermined intervals, and analyze the plasma *e.g.*, via Enzyme-Linked Immunosorbent Assay ("ELISA"), to determine concentration of the conjugate, until concentration was no longer measurable. The half-life may be calculated via a non-compartmental pharmacokinetic analysis (*e.g.*, using WINNonLin software version 4.1). In addition to the last time at which the conjugate concentration was measurable (t_f), the analysis includes observation or calculation of the following main parameters: λ_z, apparent terminal rate constant associated to the apparent terminal phase, estimated by linear regression analysis of the logarithm of the plasma concentrations versus time in the monoexponential terminal part of the curve, $t_{1/2,z}$, apparent terminal half-life, calculated according to the following equation: $t_{1/2,z}=\ln(2)/\lambda_z$; AUC, area under the plasma concentration-time curve from time zero to infinity; AUC/D, area under the plasma concentration-time curve per unit of dose; MRT, mean residence time calculated as the ratio between the area under the first moment curve, AUMC, and AUC; CL, systemic clearance, calculated as CL=D/AUC; and V_{ss}, steady state volume of distribution, calculated as V_{ss}=CL*MRT.

[0065] A further aspect of the present invention relates to a composition comprising the protein conjugate and a carrier. Broadly, the carrier may be a culture medium or a matrix (*e.g.*, a purification matrix). In some embodiments, the carrier is a pharmaceutically acceptable carrier, in which case the composition is useful for preventing or treating disorders and/or diseases in a human or animal, most preferably in a mammal, or for diagnostic purposes. As an active ingredient of the composition, the protein conjugate is preferably in a soluble form.

[0066] Generally, the composition comprises a pharmaceutically effective amount of the protein conjugate which achieves the desired effect *e.g.*, therapeutic or diagnostic.

Pharmaceutically effective amounts can be estimated from cell culture assays. For example, a dose can be formulated in animal models to achieve a circulating concentration range that includes or encompasses a concentration point or range having the desired effect in an *in vitro* system. See, *e.g.*, Molineux, *et al.*, Exp. Hematol. *27*:1724-34 (1999). This information can thus be used to accurately determine the doses in other mammals, including humans and animals. In general, dosage amounts range from about 1 ng/kg to about 10 mg/kg based on weight of the subject.

[0067] Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or in experimental animals. See, *e.g.*, Molineux, *et al.*, Exp. Hematol. *27*:1724-34 (1999). For example, the LD50 (the dose lethal to 50% of the population) as well as the ED50 (the dose therapeutically effective in 50% of the population) can be determined using methods known in the art. The dose ratio between toxic and therapeutic effects is the therapeutic index that can be expressed as the ratio between LD50 and ED50 compounds that exhibit high therapeutic indices.

[0068] The data obtained from the cell culture and animal studies can be used in formulating a range of dosage of such compounds which lies preferably within a range of circulating concentrations that include the ED50 with little or no toxicity.

[0069] The compositions can be administered via any suitable route such as locally, orally, systemically, intravenously, intramuscularly, mucosally, transdermally (*e.g.*, via a patch). They may be encapsulated in liposomes, microparticles, microcapsules, nanoparticles and the like. Techniques for formulating and administering biologically active polypeptides are also disclosed in Remington: The Science and Practice of Pharmacy (Alfonso R. Gennaro, *et al.*, eds. Philadelphia College of Pharmacy and Science 2000).

[0070] In order to fully illustrate the present invention and advantages thereof, the following specific examples are given, it being understood that the same are intended only as illustrative and in no way limitative.

EXAMPLE 1

Cloning Of Chimeric DNA Molecule

[0071] For ease of downstream protein purification, it was decided that the G-CSF-polymer proteins were secreted into the cell culture medium. Prior experience using bacterial (ST2) secretion signals with various cytokine-polymer constructs showed low secretion efficiency in both prokaryotic and eukaryotic systems. However, the use of the *Schizosaccharomycen pombe* secretion signal sequence of the pho1+ acid phosphatase (PHO) for the secretion of heterologous proteins (GFP and HPV 16 E7) into a medium was known. Therefore, this secretion signal was tested with the G-CSF-polymer constructs described below in a CHO cell expression system. Also described below are the vectors that were synthesized for the production of G-CSF-polymer constructs and expression of G-CSF-polymers.

1.A. Production Of PHO x pBSK Construct

PHO x pBSK Construct

[0072] The first construct synthesized was simply the PHO leader sequence cloned into the bacterial cloning vector pBSK. The amino acid sequence of the PHO secretion signal is listed below.

M F L Q N L F L G F L A V V C A N A

[0073] The PHO secretion signal was synthesized by fusing two sets of complementary DNA oligonucleotides together and cloning them into pBSK. The most important consideration that went into the design of the oligonucleotides was that the

fusion of the leader sequence to the N-terminus of the G-CSF-polymer be direct, without any intervening sequence. This ensured that the entire secretion signal was clipped from the molecule during processing, resulting in a secreted form of G-CSF with no amino-terminal modification when compared to naturally occurring and clinically available versions of G-CSF. By preparing the constructs in this manner, not only could direct comparisons to G-CSF and PEG-G-CSF be made, but this also limited any potential immunogenicity by introducing additional amino acids into the recombinant G-CSF protein. By incorporating restriction sites into the oligonucleotides for cloning the PHO leader into pBSK, as well as the subsequent cloning G-CSF into PHO x pBSK, these requirements were satisfied. The oligonucleotides that were used are listed below.

oNDEPHO-1F: 5′- GGCCGCCATATGTTCTTGCAAAATTTATTCCTTGGCT - 3′

oNDEPHO-1R: 5′- CCAAAAAGCCAAGGAATAAATTTTGCAAGAACATATGGC -3′

oNDEPHO-2F: 5′- TTTTGGCCGTTGTTTGCGCAAACGCGTCCCGCAGGTG - 3′

oNDEPHO-2R: 5′- GATCCACCTGCGGGACGCGTTTGCGCAAACAACGG - 3′

[0074] A diagram of the PHO x pBSK vector is shown in Figure 1. The PHO leader (PhoA) was cloned into pBSK using *Not*I and *BamHI*. The sequence for mature G-CSF was cloned into this construct utilizing the *BspMI* and *BamHI* sites. This vector confers ampicillin resistance (*bla*) when grown in bacteria.

Method Of Construction

[0075] Complementary pairs of oligonucleotides (oNDEPHO-1F and oNDEPHO-1R) and (oNDEPHO-2F and oNDEPHO-2R) were phosphorylated using T4 Polynucleotide Kinase (PNK). The T4 PNK was heat-inactivated and the oligonucleotide pairs were allowed to slowly anneal on ice. The reactions were diluted in TE and used in a ligation with pBSK previously digested using *Not*I and *BamHI*. Ligation products were electroporated into Top10 competent cells and grown on LB-ampicillin plates.

Minipreps were performed on ampicillin resistant colonies to isolate DNA and diagnostic digests identified putative clones. Sequence analysis determined which of the putative clones were correct.

1.B. Production Of PHO-G-CSF-NN x pBSK Construct

PHO-G-CSF-NN x pBSK Construct

[0076] This construct resulted from the cloning of PCR amplified material corresponding to the coding sequence of mature G-CSF into the PHO x pBSK vector using *BspMI* and *BamHI*. As stated previously, the oligonucleotides used for this purpose were designed to ensure that the junction between PHO and G-CSF had no intervening sequence by utilizing the restriction enzyme *BspMI*. Furthermore, the C-terminus of G-CSF had a direct fusion of two asparagine residues (NN) and restriction sites for the enzymes *Bbs*I and *BamHI*. *Bbs*I was subsequently utilized to directly add the NNT polymer to the C-terminus of G-CSF, while *BamHI* was used to clone GCSF-NN into the vector.

[0077] The oligonucleotides that were synthesized to amplify G-CSF are as follows:

oBspMIGCSF: 5′- CGATCGACCTGCAAGTCGCGACTCCGCTGGGTCCAGCTA-3′

oGCSFBbsBam:5′-CGGGATCCGAAGACGTGTTGTTAGGCTGGGCAAGGTGGC-3′

[0078] A diagram of the PHO-G-CSF-NN x pBSK vector is shown in Figure 2. The sequence for mature G-CSF-NN was cloned into PHO x pBSK using *BspMI* (destroyed) and *BamHI*. The subsequent addition of an NNT polymer utilized the *Bbs*I and *BamHI* sites indicated on the plasmid map. This vector confers ampicillin resistance (*bla*) when grown in bacteria.

Method Of Construction

[0079] G-CSF was amplified by PCR using oBspMIGCSF and oGCSFBbsBam oligonucleotides. The ≈ 520 bp band corresponding

to mature G-CSF was excised from an agarose gel and purified. The purified fragment was digested with *BspMI* and *BamHI*, purified and ligated into PHO x pBSK cut with the same enzymes. The ligation products were electroporated into Top10 competent cells and grown on LB-ampicillin plates. Minipreps were performed on ampicillin resistant colonies to isolate DNA and diagnostic digests identified putative clones. Sequence analysis determined which of the putative clones were correct.

1.C. Production Of PHO-G-CSF-(NNT)65 x pBSK Construct

PHO-G-CSF-(NNT)65 x pBSK Construct

[0080] The amino acid composition of this polymer encodes for the consensus mammalian N-linked glycosylation site, N-X-(S/T). Therefore, the polymer may be glycosylated on the threonine residues of the polymer extension when this construct is expressed in CHO cells. The expectation was that the polymeric increase in translated product size and posttranslational modification would modulate the pK parameters of G-CSF, conferring upon the protein-enhanced half-life in serum without decreasing its biological activity.

[0081] The construction of this polymer was achieved using an oligonucleotide ligation/multimerization scheme. By cutting the PHO-G-CSF-NN x pBSK construct with *Bbs*I, a four base underhang (GTTG) was created in the two asparagines residues added to the C-terminus of G-CSF. By designing complementary sets of oligonucleotides that code for repeating NNT triplets as well as anneal to the GTTG underhang, it was possible to multimerize the oligonucleotides that code for 9 amino acids into longer chains. Short adaptors containing a stop codon, a *Bbs*I site for future extension of the polymer and a *BamHI* site were added in low ratios to terminate the multimerization and allow for cloning of the *Bbs*I-*BamHI* polymer fragment into PHO-G-CSF-NN x pBSK.

[0082] The oligonucleotides used to synthesize the (NNT)65 polymer are listed below:

Polymer Backbone Oligonucleotides

o3NNTF: 5′- CAACACCAACAATACCAACAATACAAA-3′

o3NNTR: 5′- GTTGTTTGTATTGTTGGTATTGTTGGT-3′

Adaptor Oligonucleotides

oDent3F: 5′-CAACTAGTCTTCG-3′

oDent3R: 5′-GATCCGAAGACTA-3′

[0083] The following sequence (NTNNTNNTN) was the repeating unit of the NNT polymer that was produced using the polymer backbone oligonucleotides of o3NNTF and o3NNTR, which show a CAAC overhang and GTTG underhang respectively that were used to multimerize the polymer.

```
        N T N N T N N T N
5′-C AAC ACC AAC AAT ACC AAC AAT ACA AA-3′      (o3NNTF)
     3′-TGG TTG TTA TGG TTG TTA TGT TTG TTG-5′   (o3NNTR)
```

[0084] The following is the terminating adaptor molecule that completed the polymer and included a stop codon, *Bbs*I site for future extension of the polymer and a *BamH*I site that is necessary for cloning.

Terminating Adaptor Molecule

```
     N   *
5′-C AAC TAG TCT TCG-3′        (oDent3F)
      3′-ATC AGA AGC CTA G-5′  (oDent3R)
           BbsI   BamHI
```

[0085] A diagram of the PHO-G-CSF-NNT65 x pBSK vector is shown in Figure 3. The addition of NNT65 polymer utilized the *Bbs*I site (destroyed) that was located at the C-terminus of G-CSF and *BamH*I. As shown in Figure 3, the *Bbs*I site was

regenerated at the end of the NNT65 polymer for future extension of length. This vector confers ampicillin resistance (*bla*) when grown in bacteria.

Method Of Construction

[0086] Complementary pairs of polymer backbone oligonucleotides (o3NNTF and o3NNTR) and adaptor oligonucleotides (oDent3F and oDent3R) were phosphorylated using T4 PNK. The T4 PNK was heat-inactivated and the oligonucleotide pairs were allowed to slowly anneal on ice. Polymer multimerization was performed by mixing polymer and adaptor duplexes at 20:1 and 40:1 ratios with T4 Ligase. The T4 ligase was heat-inactivated and the entire ligation reactions were digested with *BamHI* overnight. Both reactions were precipitated and ran on an acrylamide gel. Material between 250 bp - 800 bp was excised and gel purified.

[0087] This material was used in a ligation with PHO-G-CSF-NN x pBSK that had been digested with *Bbs*I and *BamHI*. Chemically competent *Stbl2* cells were transformed with the ligation products and grown on LB-ampicillin plates. Minipreps were performed to isolate DNA and diagnostic digests identified putative clones. Sequence analysis determined which of the putative clones were correct.

[0088] The longest clone isolated from this strategy was PHO-G-CSF-NNT65 x pBSK.

1.D. Production Of PHO-G-CSF-(NNT)155 x pBSK Construct

PHO-G-CSF-(NNT)155 x pBSK Construct

[0089] The construction of this clone required the addition of additional NNT residues to the PHO-G-CSF-(NNT)65 x pBSK construct using the same oligomerization scheme. The nucleotide composition of the oligonucleotides used in this extension was altered to identify the junction between the original polymer and the extension. These alterations

maintained the original NNT composition of the polymer and utilized the same GTTG underhang and CAAC overhang strategy. By digesting PHO-GCSF-(NNT)65 with *Bbs*I and *BamHI*, it was possible to extend the length of the polymer using the same oligonucleotide multimerization strategy as before.

[0090] The oligonucleotides used to extend the (NNT)65 polymer to (NNT)155 are listed below:

Polymer Backbone Oligonucleotides

o3NNTextF: 5′- CAACACCAATAATACCAACAATACAAA-3′

o3NNTextR: 5′- GTTGTTTGTATTGTTGGTATTATTGGT-3′

Adaptor Oligonucleotides

oDent3F: 5′-CAACTAGTCTTCG-3′

oDent3R: 5′-GATCCGAAGACTA-3′

[0091] As with the production of the PHO-G-CSF-(NNT)65 x pBSK Construct, NTNNTNNTN was the repeating unit of the NNT polymer extension that was produced using the polymer backbone oligonucleotides of o3NNTextF and o3NNTextR, in which the CAAC overhang and GTTG underhang were still used to multimerize the polymer and the amino acid composition was unchanged from the original NNT65 polymer.

N T N N T N N T N

5′-C AAC ACC AA<u>T</u> AAT ACC AAC AAT ACA AA-3′ (o3NNTextF)

3′-TGG TT<u>A</u> TTA TGG TTG TTA TGT TTG TTG-5′ (o3NNTextR)

[0092] The above underlined nucleotides of o3NNTextF and o3NNTextR differed from the nucleotides in the same position in o3NNTF and o3NNTR respectively.

[0093] The following is the terminating adaptor molecule that completed the NNT155 polymer and included the *BamHI* site

necessary for cloning. oDent3F and oDent3F are the same oligonucleotides that were used for the initial NNT65 polymer.

Terminating Adaptor Molecule

N *

5′-C AAC TAG TCT TCG-3′ (oDent3F)

3′-ATC AGA AGC CTA G-5′ (oDent3R)

*Bbs*I *BamH*I

[0094] A diagram of the PHO-G-CSF-(NNT)155 x pBSK vector is shown in Figure 4. The extension of the NNT65 polymer by 90AA utilized the *Bbs*I site (destroyed) that was located at the C-terminus of PHO-G-CSF-NNT65 x pBSK and *BamH*I. It was noted that the *Bbs*I site was regenerated at the end of the NNT155 polymer for future extension of length. This vector confers ampicillin resistance (*bla*) when grown in bacteria.

Method Of Construction

[0095] Complementary pairs of polymer backbone oligonucleotides o3NNTextF and o3NNTextR, and adaptor oligonucleotides oDent3F and oDent3R were phosphorylated using T4 PNK. The T4 PNK was heat-inactivated and the oligonucleotide pairs were allowed to slowly anneal on ice. Polymer oligimerization was performed by mixing polymer and adaptor duplexes at 20:1 and 40:1 ratios with T4 Ligase. The T4 Ligase was heat-inactivated and the entire ligation reactions were digested with *BamH*I overnight. Both reactions were precipitated and ran on an acrylamide gel. Material between 250 bp to 800 bp was excised and gel purified. This material ligated into PHO-G-CSF-NNT65 x pBSK digested with *Bbs*I and *BamH*I. Chemically competent Stbl2 cells were transformed with the ligation products and grown on LB-ampicillin plates. Minipreps were performed to isolate DNA and diagnostic digests identified putative clones. Sequence analysis determined which of the putative clones were correct.

[0096] The longest clone isolated from this strategy was PHO-G-CSF-(NNT)155 x pBSK.

EXAMPLE 2

Transformation Of Host Cell And Expression Of Chimeric DNA Molecule

2.A. Production Of PHO-G-CSF-(NNT)155 x pCE2 Construct

Preparation Of Vector pCE2

[0097] The plasmid pCE2 was derived from the plasmid pREP7b, through the following manipulations. First, the 2000 bp EBNA coding region was deleted. Next, pBR322ori was replaced with pKS-ori. Then, the RSV promoter region was replaced by the CMV enhancer and the elongation factor-1a (EF-1a) promoter and intron.

[0098] The CMV enhancer was derived from a 380 bp *Xba*I-*Sph*I fragment produced by the polymerase chain reaction (PCR) from pCEP4 (Invitrogen, San Diego, CA) using the following primers:

5'-GGCTCTAGAT ATTAATAGTA ATCAATTAC-3'; and

5'-CCTCACGCAT GCACCATGGT AATAGC-3'.

[0099] The EF-1a promoter and intron (Uetsuki, *et al.*, J. Biol. Chem. *264*:5791-5798 (1989)) were derived from a 1200 bp *Sph*I-*Asp*718I fragment produced by PCR from human genomic DNA using the following primers:

5'-GGTGCATGCG TGAGGCTCCG GTGC-3'; and

5'-GTAGTTTTCACGGTACCTGAAATGGAAG-3'.

[0100] The two fragments were ligated into a *Xba*I/*Asp*718I digested vector derived from pREP7b to generate pCE2.

PHO-G-CSF-(NNT)155 x pCE2 Construct

[0101] In order to express PHO-G-CSF-(NNT)155 in mammalian cells, it was necessary to move the construct into the vector pCE2. This vector contained the minimal promoter and the first intron for the human elongation factor-1-α flanked by the immediate-early CMV enhancer. The vector also contained the hygromycin B resistance marker for mammalian selection.

[0102] A diagram of the PHO-G-CSF-(NNT)155 x pCE2 vector is shown in Figure 5. The promoter that drives expression in CHO cells is Pcmv/ef-1a. The vector was linearized for electroporation into CHO cells using *Sal*I. This vector confers resistance to hygromycin B in mammalian cells and ampicillin resistance (*bla*) when grown in bacteria.

Method Of Construction

[0103] This construct was produced by isolating and gel purifying the 1100 bp *Not*I-*BamH*I fragment from PHO-G-CSF-(NNT)155 x pBSK. This material was ligated into pCE2 that had been digested with *Not*I and *BamH*I. Chemically competent Stbl2 cells were transformed with the ligation products and grown on LB-ampicillin plates. Minipreps were performed to isolate DNA and diagnostic digests identified putative clones. Large-scale maxipreps were performed to isolate microgram quantities of the plasmid for CHO cell transformation.

2.B. Production Of Transfectant Cell Lines

[0104] In order to produce the polymers described above, mammalian cells were used as host cells for expression. In this instance, Chinese hamster ovary (CHO) cell lines were chosen. CHO cells are widely used in the pharmaceutical industry to express recombinant protein therapeutics including G-CSF and EPO. As described below, expression cultures of G-CSF-polymer constructs in CHO cells were established.

Establishment Of Adherent Cultures

[0105] The PHO-G-CSF-(NNT)155 x pCE2 vector was linearized using the enzyme *Sal*I. The digest was precipitated and re-suspended in 50 µL of TE. One (1) µg of this plasmid was used in an electroporation along with 5 x 10^6 CHO cells. Adherent CHO cells were grown in Ham's Nutrient Mixture F-12 (F-12 Ham's media) containing 10% FBS. The cells were allowed to recover overnight, and the next day media containing 700 µg/mL of hygromycin B was added to begin selection of resistant cells. The media was changed every 2-3 days as needed over the course of 2-3 weeks. Bulk pools of resistant cells were isolated and passaged two additional times in the presence of hygromycin B.

[0106] To test these cells for the secretion of PHO-G-CSF-(NNT)155 into the media, the cells were grown in Ham's media containing low serum media (0.5%) for 3-5 days. The media was isolated and used in Western blots that were probed using a polyclonal antibody against G-CSF. The blots are reproduced in Figures 6 and 7. The difference between the blots is that the samples in Figure 7 were additionally subjected to Peptide:N Glycosidase F (PNGase F) treatment. As shown in Figure 6, the blots showed immunoreactive material migrating at apparent molecular weight ≈ 95 kDa. As shown in Figure 7, digestion of these same samples with PNGase F, a glycosidase that removes N-linked glycosylation chains, reduced the immunoreactive material to apparent molecular weight ≈ 49 kDa. This corresponded approximately to the theoretical size of unmodified G-CSF-(NNT)155 protein. Native G-CSF migrates electrophoretically at ≈ 18 kDa; the addition of the NNT polymer to the C-terminus adds substantial mass to the recombinant, polymeric molecule. The expression also appeared quite stable; no appreciable proteolytic degradation was observed for the unpurified protein present in conditioned medium. Further, as shown in Figure 7, the decrease in size of the constructs after PNGase F treatment suggested the

recombinant protein constructs were subject to a substantial amount of glycosylation.

Establishment Of Suspension Cultures

[0107] To facilitate purification of G-CSF-(NNT)155 found in the conditioned media of established CHO cultures, cells were grown in a chemically defined, low protein, serum-free media (PROCHO4-CDM, Cambrex). In the process of adapting the cells to this media, the cells adapted from adherent to suspension growth.

[0108] Cells were grown in F-12 Ham's + 10% FBS to near confluency in T-185 flasks, trypsinized and suspended in PROCHO4-CDM media. 107 cells were added to 50 mL of PROCHO4-CDM and incubated in T-185 flasks. After 4-5 passages, approximately 90% of the cells were no longer adherent and grew as a mixture of single cell and aggregated cell clumps. For conditioned media collections, typically 60 mL of fresh PROCHO4-CDM media was incubated with 7-8 mL of a high cell density culture for 5-6 days. Cells were removed from the media by centrifugation and the media was subsequently clarified using a 0.2 micron filter. The media was quantitated for yield of G-CSF-(NNT)155 by western blot (typically 100-200 µg/L) and stored until needed.

2.C. Expression Of G-CSF-NNT Constructs In PROCHO4-CDM

[0109] Samples were conditioned media from the foregoing bulk CHO cell lines grown for 6 days in PROCHO4-CDM. Western blots were probed using polyclonal antibody against G-CSF. As shown in Figure 8, the size of both constructs were the same as was seen in Ham's media (as described above) and there was no degradation observed in the G-CSF(NNT)155 cell lines.

2.D. Optimization Of Expression

[0110] Various chemical and nutrient additives as well as various environmental parameters were tested in an attempt to

determine growth conditions necessary to maximize expression of the desired product. The following approaches resulted in an increase in protein accumulation.

Chemical Additives

[0111] Although it was known that not all chemical additives result in an increase in protein production, published literature indicated that the addition of adenosine or AMP to 2.5 mM leads to cell cycle arrest; effectively prolonging cell culture viability with a concomitant increase in protein accumulation. The effect of AMP was tested on CHO-mediated production of G-CSF-(NNT)155 production in ProCHO4 chemically defined medium (CDM). AMP was added at a final concentration of 1 mM in ProCHO4 CDM. No decrease in cell viability compared to control was observed. The addition of AMP resulted in a slight increase in protein production.

Environmental Parameters

Temperature Changes

[0112] Reduced incubation temperatures for CHO cultures can lead to markedly enhanced levels of protein production. As was found with other protein production enhancement methods, the observed effect is due to enhanced protein production during cell cycle arrest. The effect of reducing the incubation temperature of the recombinant CHO line from 37°C to 28°C was examined. Although cultures maintained at 28°C remained viable considerably longer than those at 37°C, the lower temperature did not result in higher recombinant protein production.

Adaptation To Suspension Culture

[0113] The bulk CHO population was converted to spinner flask culture conditions. Adaptation to suspension culture was mediated by growth in ProCHO4 CDM. Following adaptation, cells were expanded in T-flasks and seeded into spinner flasks

containing ProCHO5 CDM at various densities. A marked increase in protein production was observed during adaptation to suspension culture in ProCHO5 CDM, regardless of whether the cells were grown in static or spinner cultures.

Use Of Different Cell Lines As Hosts

[0114] One approach to optimization of expression may be to use a new cell line for host cells. Accordingly, a new shipment of CHO-K1 from ATCC was obtained. The new population was propagated and banked at an early passage for future use. This defined culture was used to generate stable clonal cell lines expressing the recombinant protein of interest. Briefly, CHO-K1 cells were electroporated with the vector of interest and selected for stable expression of hygromycin. 92 colonies were isolated and evaluated for expression of the recombinant protein of interest. Many of these colonies exhibited expression levels that were markedly higher than that of the original transfected population, described above.

Results

[0115] A very slight enhancement of expression was observed when cultures were treated with 1 mM AMP. Reduced culture temperatures increased the longevity of the cultures, but there was no enhancement of protein expression. Adaptation to suspension culture conditions in ProCHO5 CDM dramatically enhanced expression of the recombinant protein. Also, isolated clones from an ATCC-defined CHO-K1 cell line expressed the desired protein at significantly higher levels than the originally isolated population.

Example 3

Pharmacokinetic Evaluation Of G-CSF-(NNT)155 Conjugate

[0116] The pharmacokinetic parameters of the G-CSF-(NNT)155 protein conjugate was evaluated. Three other compounds were included as positive controls. The controls were Neulasta

(PEG-G-CSF), Neupogen (rh-G-CSF) and G-CSF compounds. The compounds were tested by single intravenous (i.v.) administration to mice and blood was collected up to 72 hours post-dosing. The plasma was analyzed by the ELISA method.

3.A. Analytical Method

[0117] The assay employed the quantitative sandwich enzyme immunoassay technique. A monoclonal antibody specific for G-CSF had been pre-coated onto a microplate. Standards and samples were pipetted into the wells. Any G-CSF present was bound by the immobilized antibody. After washing away any unbound substances, an enzyme-linked polyclonal antibody specific for G-CSF was added to the wells. Following a wash to remove any unbound antibody-enzyme reagent, a substrate solution was added to the wells and color developed in proportion to the amount of G-CSF bound in the initial step. The color development was stopped and the intensity of the color was measured.

Reagents

[0118] The following reagents and material were used:

- G-CSF Microplate: 96 well polystyrene microplate (12 strips of 8 wells) coated with a murine monoclonal antibody against G-CSF.
- G-CSF conjugate: 21 mL of polyclonal antibody against G-CSF conjugated to horseradish peroxidase, with preservative.
- G-CSF standard: 2 vials (25 ng/mL) of recombinant human G-CSF in a buffered protein base with preservative, lyophilized.
- Assay Diluent RD1A: 11 mL of a buffered protein base with preservative.

- Calibrator Diluent RD5: 21 mL of a buffered protein base with preservative. For cell culture supernate samples.
- Calibrator Diluent RD6A: 21 mL of animal serum with preservative. For serum/plasma samples.
- Wash Buffer Concentrate: 21 mL of a 25-fold concentrated solution of buffered surfactant with preservative.
- Color Reagent A: 12.5 mL of stabilized hydrogen peroxide.
- Color Reagent B: 12.5 mL of stabilized chromogen (tetramethylbenzidine).
- Stop Solution: 6mL of 2N sulfuric acid.
- Plate Covers: 4 adhesive strips.

Reagent Preparation

[0119] 20 mL of Wash Buffer Concentrate was diluted into deionized or distilled water to prepare 500 mL of Wash Buffer. The G-CSF Standard was reconstituted with 1 mL deionized or distilled water. This reconstitution produced a stock solution of 25000 pg/mL. The G-CSF standard was allowed to sit for a minimum of 15 minutes with gentle agitation prior to making dilutions. Nine hundred (900) µL of Calibrator Diluent RD6A was pipetted into a 2500 pg/mL tube. 600 µL of the same diluent was pipetted into the remaining 4 tubes. The stock solution was used to produce a dilution series: 25000 pg/mL (1:10) → 2500 pg/mL and 25000 pg/mL (1:3) → 833.3 pg/mL (1:3) → 277.8 pg/mL (1:3) → 92.6 pg/mL (1:3) → 30.9 pg/mL. Each tube was mixed thoroughly before the next transfer. The 2500 pg/mL standard served as the high standard. The Calibrator Diluent RD6A served as the zero standard (0 pg/mL). The standard curve was performed with 6 point: 2500-833.3-

277.8-92.6-30.9-0 pg/mL, double well for each point. For the substrate solution, Color Reagent A and B was mixed together in equal volumes within 15 minutes of use. The reagents were protected from light.

Assay Procedure

[0120] All reagents and samples were brought to room temperature before use. All reagents and working standards were prepared. One hundred (100) µL of Assay Diluent RD1A were added to each well, 100 µL of standard and an appropriate volume of sample were also added to each well. The wells were covered with an adhesive strip and incubated for 2h at room temperature. Each well was aspirated and washed with 400 µL of wash buffer, which was repeated twice for a total of three washes. After the last wash, any remaining wash buffer was removed by aspirating or decanting. The plate was inverted and blotted against clean paper towels. 200 µL of G-CSF conjugate was added to each well. The wells were covered with a new adhesive strip. The wells were incubated for 2h at room temperature. The aspiration/wash described above was repeated. Two hundred (200) µL of Substrate Solution was added to each well. The wells were incubated for 20 min. at room temperature. The wells were protected from light. Then, 50 µL of stop solution were added to each well. Finally, the optical density of each well within 30 min. was determined using a microplate reader (VersaMax -Molecular Device) set to 450nm with correction to 570nm (OD 450nm - OD 570nm).

Pharmacokinetic Analysis

[0121] A non-compartmental pharmacokinetic analysis (WINNonLin software version 4.1) was applied. The following main parameters were observed or calculated for each GCSF construct: t_f, last time at which each compound concentration was measurable; λ_z, apparent terminal rate constant associated to the apparent terminal phase, estimated by linear regression

analysis of the logarithm of the plasma concentrations versus time in the mono-exponential terminal part of the curve; $t_{1/2,z}$, apparent terminal half-life, calculated according to the following equation: $t_{1/2,z}=\ln(2)/\lambda_z$; AUC, area under the plasma concentration-time curve from time zero to infinity; AUC/D, area under the plasma concentration-time curve per unit of dose; MRT, mean residence time calculated as the ratio between the area under the first moment curve, AUMC, and AUC; CL, systemic clearance, calculated as CL=D/AUC; and V_{ss}, steady state volume of distribution, calculated as $V_{ss}=CL*MRT$.

Results

[0122] As shown in Table 9, pharmacokinetic studies in mice showed that G-CSF-(NNT)155 possessed a longer half-life (6.2h) than either the G-CSF Control (1.53h), NEUPOGEN compound (1.13h) or the NEULASTA compound (3.04h). G-CSF-(NNT)155's longer half-life corresponded to a more sustained duration of effect compared to all three controls. A corresponding substantial decrease of systemic clearance was observed for G-CSF-(NNT)155, accounting for the 9.5 mL/h/kg systemic clearance. Other conjugates containing amino acid extensions disclosed herein exhibited a decreased half-life relative to control.

Example 4

Bioavailability And Efficacy Of G-CSF-(NNT)155 Conjugate

[0123] Neutropenia, a low absolute count of neutrophils, is a serious condition that can impede the fight against infections. To stimulate a peripheral increase in neutrophil counts, granulocyte colony stimulating factor (G-CSF) may be used as a therapy for neutropenia or in combination with other stimulating factors in collection of cells for transplant. The bioavailability of partially purified G-CSF-(NNT)155, PEG-G-CSF (NEULASTA) and rh-G-CSF (NEUPOGEN) was determined and compared via i.v. (intravenous) and s.c. (subcutaneous)

administration. The NEUPOGEN compound is a recombinant methionyl human G-CSF. The NEULASTA compound is a covalent conjugate of recombinant methionyl human G-CSF and monomethoxypolyethylene glycol. As described above, G-CSF-(NNT)155 is an amino acid lengthened and/or glycosylated form of G-CSF.

4.A. Testing For Bioavailability Through ELISA

[0124] To evaluate the bioavailability of G-CSF-(NNT)155, an ELISA analysis was performed on plasma samples obtained from mice that were given doses of G-CSF-(NNT)155, PEG-G-CSF and rh-G-CSF through i.v. and s.c. administration.

[0125] Test and control articles were as follows: partially purified G-CSF-(NNT)115, PEG-G-CSF (NEULASTA), rh-G-CSF (NEUPOGEN) and the vehicle control (150 mM NaCl + 20 mM NaOAc + 0.004% Tween-20); each manufactured in a manner that was acceptable for use in animals via the designated routes of administration, i.v. and s.c.

[0126] Mice were given doses of G-CSF-(NNT)155, PEG-G-CSF, rh-G-CSF (each in the amount of 125 µg/kg) and a vehicle control through i.v and s.c. administration. Mouse plasma samples were isolated. If required, the mouse plasma samples were diluted.

[0127] Then, the mouse samples were analyzed with G-CSF ELISA. The main purpose of analyzing the plasma samples via ELISA was for qualitative purposes only, and not for quantitative purposes (*i.e.*, not to obtain extremely precise blood plasma level concentrations). The G-CSF ELISA results either provided a qualitative affirmation that the test article was present in the plasma or a qualitative repudiation that the test article was not in the plasma. The plasma samples were analyzed in triplicate, using two dilutions.

[0128] The results were that intravenously administered G-CSF-(NNT)155 could be detected out to 72 hours, whereas PEG-G-CSF could only be detected out to 24 hours. In addition, both subcutaneously administered G-CSF-(NNT)155 and PEG-G-CSF could be detected out to 72 hours. Subcutaneously administered rh-G-CSF could be detected at the 15-minute and 2-hour sampling time points.

4.B. A Single Dose Comparison Of G-CSF-(NNT)155 and PEG-G-CSF On The Hematopoietic Effects In Mice

[0129] In another evaluation of the bioavailability and efficacy of G-CSF-(NNT)155, hematology analysis involving white blood cell and neutrophil count measurements was performed on plasma samples obtained from mice that were given doses of G-CSF-(NNT)155, PEG-G-CSF and rh-G-CSF through i.v. and s.c. administration.

[0130] Test and control articles were the same as for the above G-CSF ELISA evaluation. The procedures for obtaining plasma samples were also the same as for the G-CSF ELISA evaluation. Hematology analysis results were as follows.

[0131] The white blood cell count mean data for the vehicle control ranged from 0.76 x 10^3/μL to 4.35 x 10^3/μL and 1.27 x 10^3/μL to 4.25 x 10^3/μL for the i.v. and s.c. administration, respectively. The mean absolute neutrophil count data for the vehicle control ranged from 0.11 x 10^3/μL to 0.55 x 10^3/μL and 0.29 x 10^3/μL to 0.35 x 10^3/μL for the for i.v. and s.c. administration, respectively.

[0132] The mean white blood cell count for G-CSF-(NNT)155 increased from 1.44 x 103/μL, 15 minutes post-dose to 11.45 x 10^3/μL, 72 hours post i.v. administration. The mean white blood cell count for G-CSF-(NNT)155 increased from 3.15 x 10^3/μL, 15 minutes post-dose to 11.45 x 10^3/μL, 72 hours post s.c. administration. Similarly, mean absolute neutrophil count data for G-CSF-(NNT)155 increased from 0.04 x 10^3/μL, 15

minutes post-dose to 4.24 x $10^3/\mu L$, 72 hours post i.v. administration. The mean absolute neutrophil count for G-CSF-(NNT)155 increased from 0.25 x $10^3/\mu L$, at 15 minutes post-dose to 2.04 x $10^3/\mu L$, at 72 hours post administration and decreasing to 0.14 x $10^3/\mu L$ for the s.c. route of administration at 120 hours post administration.

[0133] The mean white blood cell count for PEG-G-CSF (Neulasta) increased from 1.36 x $10^3/\mu L$, at 15 minutes post-dose to 6.03 x $10^3/\mu L$, at 24 hours post administration, and then decreased to 3.01 x $10^3/\mu L$, at 72 hour post i.v. administration. The mean white blood cell count for PEG-G-CSF (Neulasta) increased from 1.47 x $10^3/\mu L$, at 15 minutes post-dose to 4.58 x $10^3/\mu L$, at 24 hours post administration, and then decreased to 2.47 x $10^3/\mu L$, at 120 hours post s.c. administration. The mean absolute neutrophil count for PEG-G-CSF (Neulasta) increased from 0.05 x $10^3/\mu L$, at 15 minutes post-dose to 1.83 x $10^3/\mu L$, at 24 hours post administration, and then decreased to 0.20 x $10^3/\mu L$, at 72 hours post i.v. administration. The mean absolute neutrophil count for PEG-G-CSF (Neulasta) increased from 0.18 x $10^3/\mu L$, at 15 minutes post-dose to 1.04 x $10^3/\mu L$, at 24 hours post administration and then decreased to 0.22 x $10^3/\mu L$, 120 hours post s.c. administration.

[0134] The mean white blood cell count for rh-G-CSF (Neupogen) decreased from 1.30 x $10^3/\mu L$, at 15 minutes post-dose to 1.19 x $10^3/\mu L$ at 2 hours post s.c. administration. The mean absolute neutrophil count for rh-G-CSF (Neupogen) increased from 0.11 x $10^3/\mu L$, at 15 minutes post-dose to 0.49 x $10^3/\mu L$ at 2 hours post s.c. route of administration.

[0135] The result showed that intravenous administration of G-CSF-(NNT)155 demonstrated a substantial increase in white blood cell counts, through 72 hours post-dose, which correlated directly to an increase in absolute neutrophil counts. This mean increase exceeded the white blood cell

count of the vehicle control by approximately 260%. Similarly, a mean increase in the white blood cell count for the s.c. administration of G-CSF-(NNT)155 exceeded that of both the vehicle control and PEG-G-CSF by approximately 295%, 72 hours post-dose. However, both the mean white blood cell count and the mean absolute neutrophil count returned to that of both the vehicle control and PEG-G-CSF at 120 hours post-dose.

[0136] In some embodiments, the peptide contains the sequence NNT, NNNNT or NNNNNT, and n is an integer of about 150 to about 160. In some of these embodiments, the biologically active protein is G-CSF.

[0137] All publications cited in the specification are indicative of the level of skill of those skilled in the art to which this invention pertains. All these publications are herein incorporated by reference to the same extent as if each individual publication were specifically and individually indicated as being incorporated by reference.

[0138] Although the invention herein has been described with reference to particular embodiments, it is to be understood that these embodiments are merely illustrative of the principles and applications of the present invention. It is therefore to be understood that numerous modifications may be made to the illustrative embodiments and that other arrangements may be devised without departing from the spirit and scope of the present invention as defined by the appended claims.

TABLE 1

NNT, TNN, NTN, NNNT, TNNN, NTNN, NNTN, NNNNT, TNNNN, NTNNN, NNTNN, NNNTN, NNNTT, TTNNN, TNTNN, TNNTN, TNNNT, NTTNN, NTNTN, NTNNT, NNTTN, NNTNTN, NNTNNT, NNNTTN, NNNTNT, NNNNTTT, TTTNNNN, TNTTNNN, TNTNTNN, TNTNNTN, TNTNNNT, TNNTTNN, TNNTNTN, TNNTNNT, TNNNTNT, TNNNTTN, TNNNNTT, TTNTNNN, TTNNTNN, TTNNNTN, TTNNNNT, NTTTNNN, NTTNTNN, NTTNNTN, NTTNNNT, NTNTTNN, NTNNTTN, NTNNNTT, NTNTNTN, NTNTNNT, NTNNTNT, NNTTTNN, NNTTNTN, NNTTNNT, NNTNTTN, NNTNTNT, NNTNNTT, NNNTTTN, NNNTTNT, NNNTNTT, NNNNNTT, TTNNNNN, TNTNNNN, TNNTNNN, TNNNTNN, TNNNNTN, TNNNNNT, NTTNNNN, NTNTNNN, NTNNTNN, NTNNNTN, NTNNNNT, NNTTNNN, NNTNTNN, NNTNNTN, NNTNNNT, NNNTTNN, NNNTNTN, NNNTNNT, NNNNTTN, NNNNTNT NNNNNNT, TNNNNNN, NTNNNNN, NNTNNNN, NNNTNNN, NNNNTNN, NNNNNTN, NNA, ANN, NAN, NNNA, ANNN, NANN, NNAN, NNNNA, ANNNN, NANNN, NNANN, NNNAN, NNNAA, AANNN, ANANN, ANNAN, ANNNA, NAANN, NANAN, NANNA, NNAAN, NNANA, NNNNNA, ANNNNN, NANNNN, NNANNN, NNNANN, NNNNAN, NNNNAA, AANNNN, ANANNN, ANNANN, ANNNAN, ANNNNA, NAANNN, NANANN, NANNAN, NANNNA, NNAANN, NNANAN, NNANNA, NNNAAN, NNNANA, NNNNAAA, AAANNNN, ANAANNN, ANANANN, ANANNAN, ANANNNA, ANNAANN, ANNANAN, ANNANNA, ANNNANA, ANNNAAN, ANNNNAA, AANANNN, AANNANN, AANNNAN, AANNNNA, NAAANNN, NAANANN, NAANNAN, NAANNNA, NANAANN, NANNAAN, NANNNAA, NANANAN, NANANNA, NANNANA, NNAAANN, NNAANAN, NNAANNA, NNANAAN, NNANANA, NNANNAA, NNNAAAN, NNNAANA, NNNANAA, NNNNNAA, AANNNNN, ANANNNN, ANNANNN, ANNNANN, ANNNNAN, ANNNNNA, NAANNNN, NANANNN, NANNANN, NANNNAN, NANNNNA, NNAANNN, NNANANN, NNANNAN, NNANNNA, NNNAANN, NNNANAN, NNNANNA, NNNNAAN, NNNNANA NNNNNNA, ANNNNNN, NANNNNN, NNANNNN, NNNANNN, NNNNANN, NNNNNAN, NNS, SNN, NSN, NNNS,

SNNN, NSNN, NNSN, NNNNS, SNNNN, NSNNN, NNSNN, NNNSN, NNNSS, SSNNN, SNSNN, SNNSN, SNNNS, NSSNN, NSNSN, NSNNS, NNSSN, NNSNS, NNNNNS, SNNNNN, NSNNNN, NNSNNN, NNNSNN, NNNNSN, NNNNSS, SSNNNN, SNSNNN, SNNSNN, SNNNSN, SNNNNS, NSSNNN, NSNSNN, NSNNSN, NSNNNS, NNSSNN, NNSNSN, NNSNNS, NNNSSN, NNNSNS, NNNNSSS, SSSNNNN, SNSSNNN, SNSNSNN, SNSNNSN, SNSNNNS, SNNSSNN, SNNSNSN, SNNSNNS, SNNNSNS, SNNNSSN, SNNNNSS, SSNSNNN, SSNNSNN, SSNNNSN, SSNNNNS, NSSSNNN, NSSNSNN, NSSNNSN, NSSNNNS, NSNSSNN, NSNNSSN, NSNNNSS, NSNSNSN, NSNSNNS, NSNNSNS, NNSSSNN, NNSSNSN, NNSSNNS, NNSNSSN, NNSNSNS, NNSNNSS, NNNSSSN, NNNSSNS, NNNSNSS, NNNNNSS, SSNNNNN, SNSNNNN, SNNSNNN, SNNNSNN, SNNNNSN, SNNNNNS, NSSNNNN, NSNSNNN, NSNNSNN, NSNNNSN, NSNNNNS, NNSSNNN, NNSNSNN, NNSNNSN, NNSNNNS, NNNSSNN, NNNSNSN, NNNSNNS, NNNNSSN, NNNNSNS NNNNNNS, SNNNNNN, NSNNNNN, NNSNNNN, NNNSNNN, NNNNSNN, NNNNNSN, NNQ, QNN, NQN, NNNQ, QNNN, NQNN, NNQN, NNNNQ, QNNNN, NQNNN, NNQNN, NNNQN, NNNQQ, QQNNN, QNQNN, QNNQN, QNNNQ, NQQNN, NQNQN, NQNNQ, NNQQN, NNQNQ, NNNNNQ, QNNNNN, NQNNNN, NNQNNN, NNNQNN, NNNNQN, NNNNQQ, QQNNNN, QNQNNN, QNNQNN, QNNNQN, QNNNNQ, NQQNNN, NQNQNN, NQNNQN, NQNNNQ, NNQQNN, NNQNQN, NNQNNQ, NNNQQN, NNNQNQ, NNNNQQQ, QQQNNNN, QNQQNNN, QNQNQNN, QNQNNQN, QNQNNNQ, QNNQQNN, QNNQNQN, QNNQNNQ, QNNNQNQ, QNNNQQN, QNNNNQQ, QQNQNNN, QQNNQNN, QQNNNQN, QQNNNNQ, NQQQNNN, NQQNQNN, NQQNNQN, NQQNNNQ, NQNQQNN, NQNNQQN, NQNNNQQ, NQNQNQN, NQNQNNQ, NQNNQNQ, NNQQQNN, NNQQNQN, NNQQNNQ, NNQNQQN, NNQNQNQ, NNQNNQQ, NNNQQQN, NNNQQNQ, NNNQNQQ, NNNNNQQ, QQNNNNN, QNQNNNN, QNNQNNN, QNNNQNN, QNNNNQN, QNNNNNQ, NQQNNNN, NQNQNNN, NQNNQNN, NQNNNQN, NQNNNNQ, NNQQNNN, NNQNQNN, NNQNNQN, NNQNNNQ, NNNQQNN, NNNQNQN, NNNQNNQ, NNNNQQN, NNNNQNQ NNNNNNQ, QNNNNNN, NQNNNNN, NNQNNNN, NNNQNNN, NNNNQNN, NNNNNQN, NNE, ENN, NEN, NNNE, ENNN, NENN, NNEN, NNNNE, ENNNN, NENNN, NNENN, NNNEN, NNNEE,

EENNN, ENENN, ENNEN, ENNNE, NEENN, NENEN, NENNE, NNEEN, NNENE, NNNNNE, ENNNNN, NENNNN, NNENNN, NNNENN, NNNNEN, NNNNEE, EENNNN, ENENNN, ENNENN, ENNNEN, ENNNNE, NEENNN, NENENN, NENNEN, NENNNE, NNEENN, NNENEN, NNENNE, NNNEEN, NNNENE, NNNNEEE, EEENNNN, ENEENNN, ENENENN, ENENNEN, ENENNNE, ENNEENN, ENNENEN, ENNENNE, ENNNENE, ENNNEEN, ENNNNEE, EENENNN, EENNENN, EENNNEN, EENNNNE, NEEENNN, NEENENN, NEENNEN, NEENNNE, NENEENN, NENNEEN, NENNNEE, NENENEN, NENENNE, NENNENE, NNEEENN, NNEENEN, NNEENNE, NNENEEN, NNENENE, NNENNEE, NNNEEEN, NNNEENE, NNNENEE, NNNNNEE, EENNNNN, ENENNNN, ENNENNN, ENNNENN, ENNNNEN, ENNNNNE, NEENNNN, NENENNN, NENNENN, NENNNEN, NENNNNE, NNEENNN, NNENENN, NNENNEN, NNENNNE, NNNEENN, NNNENEN, NNNENNE, NNNNEEN, NNNNENE NNNNNNE, ENNNNNN, NENNNNN, NNENNNN, NNNENNN, NNNNENN, NNNNNEN, NNH, HNN, NHN, NNNH, HNNN, NHNN, NNHN, NNNNH, HNNNN, NHNNN, NNHNN, NNNHN, NNNHH, HHNNN, HNHNN, HNNHN, HNNNH, NHHNN, NHNHN, NHNNH, NNHHN, NNHNH, NNNNNH, HNNNNN, NHNNNN, NNHNNN, NNNHNN, NNNNHN, NNNNHH, HHNNNN, HNHNNN, HNNHNN, HNNNHN, HNNNNH, NHHNNN, NHNHNN, NHNNHN, NHNNNH, NNHHNN, NNHNHN, NNHNNH, NNNHHN, NNNHNH, NNNNHH, NNNNHHH, HHHNNNN, HNHHNNN, HNHNHNN, HNHNNHN, HNHNNNH, HNNHHNN, HNNHNHN, HNNHNNH, HNNNHNH, HNNNHHN, HNNNNHH, HHNHNNN, HHNNHNN, HHNNNHN, HHNNNNH, NHHHNNN, NHHNHNN, NHHNNHN, NHHNNNH, NHNHHNN, NHNNHHN, NHNNNHH, NHNHNHN, NHNHNNH, NHNNHNH, NNHHHNN, NNHHNHN, NNHHNNH, NNHNHHN, NNHNHNH, NNHNNHH, NNNHHHN, NNNHHNH, NNNHNHH, NNNNNHH, HHNNNNN, HNHNNNN, HNNHNNN, HNNNHNN, HNNNNHN, HNNNNNH, NHHNNNN, NHNHNNN, NHNNHNN, NHNNNHN, NHNNNNH, NNHHNNN, NNHNHNN, NNHNNHN, NNHNNNH, NNNHHNN, NNNHNHN, NNNHNNH, NNNNHHN, NNNNHNH NNNNNNH, HNNNNNN, NHNNNNN, NNHNNNN, NNNHNNN, NNNNHNN, NNNNNHN, NND, DNN, NDN, NNND, DNNN, NDNN, NNDN, NNNND, DNNNN, NDNNN, NNDNN, NNNDN, NNNDD, DDNNN, DNDNN, DNNDN, DNNND, NDDNN, NDNDN, NDNND, NNDDN,

NNDND, NNNNND, DNNNNN, NDNNNN, NNDNNN, NNNDNN, NNNNDN, NNNNDD, DDNNNN, DNDNNN, DNNDNN, DNNNDN, DNNNND, NDDNNN, NDNDNN, NDNNDN, NDNNND, NNDDNN, NNDNDN, NNDNND, NNNDDN, NNNDND, NNNNDDD, DDDNNNN, DNDDNNN, DNDNDNN, DNDNNDN, DNDNNND, DNNDDNN, DNNDNDN, DNNDNND, DNNNDND, DNNNDDN, DNNNNDD, DDNDNNN, DDNNDNN, DDNNNDN, DDNNNND, NDDDNNN, NDDNDNN, NDDNNDN, NDDNNND, NDNDDNN, NDNNDDN, NDNNNDD, NDNDNDN, NDNDNND, NDNNDND, NNDDDNN, NNDDNDN, NNDDNND, NNDNDDN, NNDNDND, NNDNNDD, NNNDDDN, NNNDDND, NNNDNDD, NNNNNDD, DDNNNNN, DNDNNNN, DNNDNNN, DNNNDNN, DNNNNDN, DNNNNND, NDDNNNN, NDNDNNN, NDNNDNN, NDNNNDN, NDNNNND, NNDDNNN, NNDNDNN, NNDNNDN, NNDNNND, NNNDDNN, NNNDNDN, NNNDNND, NNNNDDN, NNNNDND NNNNNND, DNNNNNN, NDNNNNN, NNDNNNN, NNNDNNN, NNNNDNN, and NNNNNDN.

TABLE 2

GGT, TGG, GTG, GGGT, TGGG, GTGG, GGTG, GGGGT, TGGGG, GTGGG, GGTGG, GGGTG, GGGTT, TTGGG, TGTGG, TGGTG, TGGGT, GTTGG, GTGTG, GTGGT, GGTTG, GGTGT, GGGGGT, TGGGGG, GTGGGG, GGTGGG, GGGTGG, GGGGTG, GGGGTT, TTGGGG, TGTGGG, TGGTGG, TGGGTG, TGGGGT, GTTGGG, GTGTGG, GTGGTG, GTGGGT, GGTTGG, GGTGTG, GGTGGT, GGGTTG, GGGTGT, GGGGTTT, TTTGGGG, TGTTGGG, TGTGTGG, TGTGGTG, TGTGGGT, TGGTTGG, TGGTGTG, TGGTGGT, TGGGTGT, TGGGTTG, TGGGGTT, TTGTGGG, TTGGTGG, TTGGGTG, TTGGGGT, GTTTGGG, GTTGTGG, GTTGGTG, GTTGGGT, GTGTTGG, GTGGTTG, GTGGGTT, GTGTGTG, GTGTGGT, GTGGTGT, GGTTTGG, GGTTGTG, GGTTGGT, GGTGTTG, GGTGTGT, GGTGGTT, GGGTTTG, GGGTTGT, GGGTGTT, GGGGGTT, TTGGGGG, TGTGGGG, TGGTGGG, TGGGTGG, TGGGGTG, TGGGGGT, GTTGGGG, GTGTGGG, GTGGTGG, GTGGGTG, GTGGGGT, GGTTGGG, GGTGTGG, GGTGGTG, GGTGGGT, GGGTTGG, GGGTGTG, GGGTGGT, GGGGTTG, GGGGTGT GGGGGGT, TGGGGGG, GTGGGGG, GGTGGGG, GGGTGGG, GGGGTGG, GGGGGTG, GGA, AGG, GAG, GGGA, AGGG, GAGG, GGAG, GGGGA, AGGGG, GAGGG, GGAGG, GGGAG, GGGAA, AAGGG, AGAGG, AGGAG, AGGGA, GAAGG, GAGAG, GAGGA, GGAAG, GGAGA, GGGGGA, AGGGGG, GAGGGG, GGAGGG, GGGAGG, GGGGAG, GGGGAA, AAGGGG, AGAGGG, AGGAGG, AGGGAG, AGGGGA, GAAGGG, GAGAGG, GAGGAG, GAGGGA, GGAAGG, GGAGAG, GGAGGA, GGGAAG, GGGAGA, GGGGAAA, AAAGGGG, AGAAGGG, AGAGAGG, AGAGGAG, AGAGGGA, AGGAAGG, AGGAGAG, AGGAGGA, AGGGAGA, AGGGAAG, AGGGGAA, AAGAGGG, AAGGAGG, AAGGGAG, AAGGGGA, GAAAGGG, GAAGAGG, GAAGGAG, GAAGGGA, GAGAAGG, GAGGAAG, GAGGGAA, GAGAGAG, GAGAGGA, GAGGAGA, GGAAAGG, GGAAGAG, GGAAGGA, GGAGAAG, GGAGAGA, GGAGGAA, GGGAAAG, GGGAAGA, GGGAGAA, GGGGGAA, AAGGGGG, AGAGGGG, AGGAGGG, AGGGAGG, AGGGGAG, AGGGGGA, GAAGGGG, GAGAGGG, GAGGAGG, GAGGGAG, GAGGGGA, GGAAGGG, GGAGAGG, GGAGGAG, GGAGGGA, GGGAAGG, GGGAGAG, GGGAGGA, GGGGAAG, GGGGAGA GGGGGGA, AGGGGGG, GAGGGGG, GGAGGGG, GGGAGGG, GGGGAGG, GGGGGAG, GGS, SGG, GSG, GGGS,

SGGG, GSGG, GGSG, GGGGS, SGGGG, GSGGG, GGSGG, GGGSG, GGGSS, SSGGG, SGSGG, SGGSG, SGGGS, GSSGG, GSGSG, GSGGS, GGSSG, GGSGS, GGGGGS, SGGGGG, GSGGGG, GGSGGG, GGGSGG, GGGGSG, GGGGSS, SSGGGG, SGSGGG, SGGSGG, SGGGSG, SGGGGS, GSSGGG, GSGSGG, GSGGSG, GSGGGS, GGSSGG, GGSGSG, GGSGGS, GGGSSG, GGGSGS, GGGGSSS, SSSGGGG, SGSSGGG, SGSGSGG, SGSGGSG, SGSGGGS, SGGSSGG, SGGSGSG, SGGSGGS, SGGGSGS, SGGGSSG, SGGGGSS, SSGSGGG, SSGGSGG, SSGGGSG, SSGGGGS, GSSSGGG, GSSGSGG, GSSGGSG, GSSGGGS, GSGSSGG, GSGGSSG, GSGGGSS, GSGSGSG, GSGSGGS, GSGGSGS, GGSSSGG, GGSSGSG, GGSSGGS, GGGSSSG, GGGSSGS, GGGSGSS, GGGGGSS, SSGGGGG, SGSGGGG, SGGSGGG, SGGGSGG, SGGGGSG, SGGGGGS, GSSGGGG, GSGSGGG, GSGGSGG, GSGGGSG, GSGGGGS, GGSSGGG, GGSGSGG, GGSGGSG, GGSGGGS, GGGSSGG, GGGSGSG, GGGSGGS, GGGGSSG, GGGGSGS GGGGGGS, SGGGGGG, GSGGGGG, GGSGGGG, GGGSGGG, GGGGSGG, GGGGGSG, GGQ, QGG, GQG, GGGQ, QGGG, GQGG, GGQG, GGGGQ, QGGGG, GQGGG, GGQGG, GGGQG, GGGQQ, QQGGG, QGQGG, QGGQG, QGGGQ, GQQGG, GQGQG, GQGGQ, GGQQG, GGQGQ, GGGGQQ, QQGGGG, QGQGGG, QGGQGG, QGGGQG, QGGGGQ, GQQGGG, GQGQGG, GQGGQG, GQGGGQ, GGQQGG, GGQGQG, GGQGGQ, GGGQQG, GGGQGQ, GGGGQQQ, QQQGGGG, QGQQGGG, QGQGQGG, QGQGGQG, QGQGGGQ, QGGQQGG, QGGQGQG, QGGGQGQ, QGGGGQQ, QQGQGGG, QQGGQGG, QQGGGQG, QQGGGGQ, GQQQGGG, GQQGQGG, GQQGGQG, GQQGGGQ, GQGQQGG, GQGGQQG, GQGGGQQ, GQGQGQG, GQGQGGQ, GQGGQGQ, GGQQQGG, GGQQGQG, GGQQGGQ, GGQGQQG, GGQGQGQ, GGQGGQQ, GGGQQQG, GGGQQGQ, GGGQGQQ, GGGGGQQ, QQGGGGG, QGQGGGG, QGGQGGG, QGGGQGG, QGGGGQG, QGGGGGQ, GQGGGGG, GQGQGGG, GQGGQGG, GQGGGQG, GQGGGGQ, GGQQGGG, GGQGQGG, GGQGGQG, GGQGGGQ, GGGQQGG, GGGQGQG, GGGQGGQ, GGGGQQG, GGGGQGQ GGGGGGQ, QGGGGGG, GQGGGGG, GGQGGGG, GGGQGGG, GGGGQGG, GGGGGQG, GGE, EGG, GEG, GGGE, EGGG, GEGG, GGEG, GGGGE, EGGGG, GEGGG, GGEGG, GGGEG, GGGEE,

EEGGG, EGEGG, EGGEG, EGGGE, GEEGG, GEGEG, GEGGE, GGEEG, GGEGE, GGGGGE, EGGGGG, GEGGGG, GGEGGG, GGGEGG, GGGGEG, GGGGEE, EEGGGG, EGEGGG, EGGEGG, EGGGEG, EGGGGE, GEEGGG, GEGEGG, GEGGEG, GEGGGE, GGEEGG, GGEGEG, GGEGGE, GGGEEG, GGGEGE, GGGGEEE, EEEGGGG, EGEEGGG, EGEGEGG, EGEGGEG, EGEGGGE, EGGEEGG, EGGEGEG, EGGEGGE, EGGGEGE, EGGGEEG, EGGGGEE, EEGEGGG, EEGGEGG, EEGGGEG, EEGGGGE, GEEEGGG, GEEGEGG, GEEGGEG, GEEGGGE, GEGEEGG, GEGGEEG, GEGGGEE, GEGEGEG, GEGEGGE, GEGGEGE, GGEEEGG, GGEEGEG, GGEEGGE, GGEGEEG, GGEGEGE, GGEGGEE, GGGEEEG, GGGEEGE, GGGEGEE, GGGGGEE, EEGGGGG, EGEGGGG, EGGEGGG, EGGGEGG, EGGGGEG, EGGGGGE, GEEGGGG, GEGEGGG, GEGGEGG, GEGGGEG, GEGGGGE, GGEEGGG, GGEGEGG, GGEGGEG, GGEGGGE, GGGEEGG, GGGEGEG, GGGEGGE, GGGGEEG, GGGGEGE GGGGGGE, EGGGGGG, GEGGGGG, GGEGGGG, GGGEGGG, GGGGEGG, GGGGGEG, GGH, HGG, GHG, GGGH, HGGG, GHGG, GGHG, GGGGH, HGGGG, GHGGG, GGHGG, GGGHG, GGGHH, HHGGG, HGHGG, HGGHG, HGGGH, GHHGG, GHGHG, GHGGH, GGHHG, GGHGH, GGGGGH, HGGGGG, GHGGGG, GGHGGG, GGGHGG, GGGGHG, GGGGHH, HHGGGG, HGHGGG, HGGHGG, HGGGHG, HGGGGH, GHHGGG, GHGHGG, GHGGHG, GHGGGH, GGHHGG, GGHGHG, GGHGGH, GGGHHG, GGGHGH, GGGGHHH, HHHGGGG, HGHHGGG, HGHGHGG, HGHGGHG, HGHGGGH, HGGHHGG, HGGHGHG, HGGHGGH, HGGGHGH, HGGGHHG, HGGGGHH, HHGHGGG, HHGGHGG, HHGGGHG, HHGGGGH, GHHHGGG, GHHGHGG, GHHGGHG, GHHGGGH, GHGHHGG, GHGGHHG, GHGGGHH, GHGHGHG, GHGHGGH, GHGGHGH, GGHHHGG, GGHHGHG, GGHHGGH, GGHGHHG, GGHGHGH, GGHGGHH, GGGHHHG, GGGHHGH, GGGHGHH, GGGGGHH, HHGGGGG, HGHGGGG, HGGHGGG, HGGGHGG, HGGGGHG, HGGGGGH, GHHGGGG, GHGHGGG, GHGGHGG, GHGGGHG, GHGGGGH, GGHHGGG, GGHGHGG, GGHGGHG, GGHGGGH, GGGHHGG, GGGHGHG, GGGHGGH, GGGGHHG, GGGGHGH GGGGGGH, HGGGGGG, GHGGGGG, GGHGGGG, GGGHGGG, GGGGHGG, GGGGGHG, GGN, NGG, GNG, GGGN, NGGG, GNGG, GGNG, GGGGN, NGGGG, GNGGG, GGNGG, GGGNG, GGGNN, NNGGG, NGNGG, NGGNG, NGGGN, GNNGG, GNGNG, GNGGN, GGNNG,

GGNGN, GGGGGN, NGGGGG, GNGGGG, GGNGGG, GGGNGG, GGGGNG, GGGGNN, NNGGGG, NGNGGG, NGGNGG, NGGGNG, NGGGGN, GNNGGG, GNGNGG, GNGGNG, GNGGGN, GGNNGG, GGNGNG, GGNGGN, GGGNNG, GGGNGN, GGGGNNN, NNNGGGG, NGNNGGG, NGNGNGG, NGNGGNG, NGNGGGN, NGGNNGG, NGGNGNG, NGGNGGN, NGGGNGN, NGGGNNG, NGGGGNN, NNGNGGG, NNGGNGG, NNGGGNG, NNGGGGN, GNNNGGG, GNNGNGG, GNNGGNG, GNNGGGN, GNGNNGG, GNGGNNG, GNGGGNN, GNGNGNG, GNGNGGN, GNGGNGN, GGNNNGG, GGNNGNG, GGNNGGN, GGNGNNG, GGNGNGN, GGNGGNN, GGGNNNG, GGGNNGN, GGGNGNN, GGGGGNN, NNGGGGG, NGNGGGG, NGGNGGG, NGGGNGG, NGGGGNG, NGGGGGN, GNNGGGG, GNGNGGG, GNGGNGG, GNGGGNG, GNGGGGN, GGNNGGG, GGNGNGG, GGNGGNG, GGNGGGN, GGGNNGG, GGGNGNG, GGGNGGN, GGGGNNG, GGGGNGN GGGGGGN, NGGGGGG, GNGGGGG, GGNGGGG, GGGNGGG, GGGGNGG, GGGGGNG, GGD, DGG, GDG, GGGD, DGGG, GDGG, GGDG, GGGGD, DGGGG, GDGGG, GGDGG, GGGDG, GGGDD, DDGGG, DGDGG, DGGDG, DGGGD, GDDGG, GDGDG, GDGGD, GGDDG, GGDGD, GGGGGD, DGGGGG, GDGGGG, GGDGGG, GGGDGG, GGGGDG, GGGGDD, DDGGGG, DGDGGG, DGGDGG, DGGGDG, DGGGGD, GDDGGG, GDGDGG, GDGGDG, GDGGGD, GGDDGG, GGDGDG, GGDGGD, GGGDDG, GGGDGD, GGGGDDD, DDDGGGG, DGDDGGG, DGDGDGG, DGDGGDG, DGDGGGD, DGGDDGG, DGGDGDG, DGGDGGD, DGGGDGD, DGGGDDG, DGGGGDD, DDGDGGG, DDGGDGG, DDGGGDG, DDGGGGD, GDDDGGG, GDDGDGG, GDDGGDG, GDDGGGD, GDGDDGG, GDGGDDG, GDGGGDD, GDGDGDG, GDGDGGD, GDGGDGD, GGDDDGG, GGDDGDG, GGDDGGD, GGDGDDG, GGDGDGD, GGDGGDD, GGGDDDG, GGGDDGD, GGGDGDD, GGGGGDD, DDGGGGG, DGDGGGG, DGGDGGG, DGGGDGG, DGGGGDG, DGGGGGD, GDDGGGG, GDGDGGG, GDGGDGG, GDGGGDG, GDGGGGD, GGDDGGG, GGDGDGG, GGDGGDG, GGDGGGD, GGGDDGG, GGGDGDG, GGGDGGD, GGGGDDG, GGGGDGD GGGGGGD, DGGGGGG, GDGGGGG, GGDGGGG, GGGDGGG, GGGGDGG, and GGGGGDG.

TABLE 3

QQT, TQQ, QTQ, QQQT, TQQQ, QTQQ, QQTQ, QQQQT, TQQQQ, QTQQQ, QQTQQ, QQQTQ, QQQTT, TTQQQ, TQTQQ, TQQTQ, TQQQT, QTTQQ, QTQTQ, QTQQT, QQTTQ, QQTQT, QQQQQT, TQQQQQ, QTQQQQ, QQTQQQ, QQQTQQ, QQQQTQ, QQQQTT, TTQQQQ, TQTQQQ, TQQTQQ, TQQQTQ, TQQQQT, QTTQQQ, QTQTQQ, QTQQTQ, QTQQQT, QQTTQQ, QQTQTQ, QQTQQT, QQQTTQ, QQQTQT, QQQQTTT, TTTQQQQ, TQTTQQQ, TQTQTQQ, TQTQQTQ, TQTQQQT, TQQTTQQ, TQQTQTQ, TQQTQQT, TQQQTQT, TQQQTTQ, TQQQQTT, TTQTQQQ, TTQQTQQ, TTQQQTQ, TTQQQQT, QTTTQQQ, QTTQTQQ, QTTQQTQ, QTTQQQT, QTQTTQQ, QTQQTTQ, QTQQQTT, QTQTQTQ, QTQTQQT, QTQQTQT, QQTTTQQ, QQTTQTQ, QQTTQQT, QQTQTTQ, QQTQTQT, QQTQQTT, QQQTTTQ, QQQTTQT, QQQTQTT, QQQQQTT, TTQQQQQ, TQTQQQQ, TQQTQQQ, TQQQTQQ, TQQQQTQ, TQQQQQT, QTTQQQQ, QTQTQQQ, QTQQTQQ, QTQQQTQ, QTQQQQT, QQTTQQQ, QQTQTQQ, QQTQQTQ, QQTQQQT, QQQTTQQ, QQQTQTQ, QQQTQQT, QQQQTTQ, QQQQTQT QQQQQQT, TQQQQQQ, QTQQQQQ, QQTQQQQ, QQQTQQQ, QQQQTQQ, QQQQQTQ, QQA, AQQ, QAQ, QQQA, AQQQ, QAQQ, QQAQ, QQQQA, AQQQQ, QAQQQ, QQAQQ, QQQAQ, QQQAA, AAQQQ, AQAQQ, AQQAQ, AQQQA, QAAQQ, QAQAQ, QAQQA, QQAAQ, QQAQA, QQQQQA, AQQQQQ, QAQQQQ, QQAQQQ, QQQAQQ, QQQQAQ, QQQQAA, AAQQQQ, AQAQQQ, AQQAQQ, AQQQAQ, AQQQQA, QAAQQQ, QAQAQQ, QAQQAQ, QAQQQA, QQAAQQ, QQAQAQ, QQAQQA, QQQAAQ, QQQAQA, QQQQAAA, AAAQQQQ, AQAAQQQ, AQAQAQQ, AQAQQAQ, AQAQQQA, AQQAAQQ, AQQAQAQ, AQQAQQA, AQQQAQA, AQQQAAQ, AQQQQAA, AAQAQQQ, AAQQAQQ, AAQQQAQ, AAQQQQA, QAAAQQQ, QAAQAQQ, QAAQQAQ, QAAQQQA, QAQAAQQ, QAQQAAQ, QAQQQAA, QAQAQAQ, QAQAQQA, QAQQAQA, QQAAAQQ, QQAAQAQ, QQAAQQA, QQAQAAQ, QQAQAQA, QQAQQAA, QQQAAAQ, QQQAAQA, QQQAQAA, QQQQQAA, AAQQQQQ, AQAQQQQ, AQQAQQQ, AQQQAQQ, AQQQQAQ, AQQQQQA, QAAQQQQ, QAQAQQQ, QAQQAQQ, QAQQQAQ, QAQQQQA, QQAAQQQ, QQAQAQQ, QQAQQAQ, QQAQQQA, QQQAAQQ, QQQAQAQ, QQQAQQA, QQQQAAQ, QQQQAQA QQQQQQA, AQQQQQQ, QAQQQQQ, QQAQQQQ, QQQAQQQ, QQQQAQQ, QQQQQAQ, QQS, SQQ, QSQ, QQQS,

SQQQ, QSQQ, QQSQ, QQQQS, SQQQQ, QSQQQ, QQSQQ, QQQSQ, QQQSS, SSQQQ, SQSQQ, SQQSQ, SQQQS, QSSQQ, QSQSQ, QSQQS, QQSSQ, QQSQS, QQQQQS, SQQQQQ, QSQQQQ, QQSQQQ, QQQSQQ, QQQQSQ, QQQQSS, SSQQQQ, SQSQQQ, SQQSQQ, SQQQSQ, SQQQQS, QSSQQQ, QSQSQQ, QSQQSQ, QSQQQS, QQSSQQ, QQSQSQ, QQSQQS, QQQSSQ, QQQSQS, QQQQSSS, SSSQQQQ, SQSSQQQ, SQSQSQQ, SQSQQSQ, SQSQQQS, SQQSSQQ, SQQSQSQ, SQQSQQS, SQQQSQS, SQQQSSQ, SQQQQSS, SSQSQQQ, SSQQSQQ, SSQQQSQ, SSQQQQS, QSSSQQQ, QSSQSQQ, QSSQQSQ, QSSQQQS, QSQSSQQ, QSQQSSQ, QSQQQSS, QSQSQSQ, QSQSQQS, QSQQSQS, QQSSSQQ, QQSSQSQ, QQSSQQS, QQSQSSQ, QQSQSQS, QQSQQSS, QQQSSSQ, QQQSSQS, QQQSQSS, QQQQQSS, SSQQQQQ, SQSQQQQ, SQQSQQQ, SQQQSQQ, SQQQQSQ, SQQQQQS, QSSQQQQ, QSQSQQQ, QSQQSQQ, QSQQQSQ, QSQQQQS, QQSSQQQ, QQSQSQQ, QQSQQSQ, QQSQQQS, QQQSSQQ, QQQSQSQ, QQQSQQS, QQQQSSQ, QQQQSQS QQQQQQS, SQQQQQQ, QSQQQQQ, QQSQQQQ, QQQSQQQ, QQQQSQQ, QQQQQSQ, QQE, EQQ, QEQ, QQQE, EQQQ, QEQQ, QQEQ, QQQQE, EQQQQ, QEQQQ, QQEQQ, QQQEQ, QQQEE, EEQQQ, EQEQQ, EQQEQ, EQQQE, QEEQQ, QEQEQ, QEQQE, QQEEQ, QQEQE, QQQQQE, EQQQQQ, QEQQQQ, QQEQQQ, QQQEQQ, QQQQEQ, QQQQEE, EEQQQQ, EQEQQQ, EQQEQQ, EQQQEQ, EQQQQE, QEEQQQ, QEQEQQ, QEQQEQ, QEQQQE, QQEEQQ, QQEQEQ, QQEQQE, QQQEEQ, QQQEQE, QQQQEEE, EEEQQQQ, EQEEQQQ, EQEQEQQ, EQEQQEQ, EQEQQQE, EQQEEQQ, EQQEQEQ, EQQEQQE, EQQQEQE, EQQQEEQ, EQQQQEE, EEQEQQQ, EEQQEQQ, EEQQQEQ, EEQQQQE, QEEEQQQ, QEEQEQQ, QEEQQEQ, QEEQQQE, QEQEEQQ, QEQQEEQ, QEQQQEE, QEQEQEQ, QEQEQQE, QEQQEQE, QQEEEQQ, QQEEQEQ, QQEEQQE, QQEQEEQ, QQEQEQE, QQEQQEE, QQQEEEQ, QQQEEQE, QQQEQEE, QQQQQEE, EEQQQQQ, EQEQQQQ, EQQEQQQ, EQQQEQQ, EQQQQEQ, EQQQQQE, QEEQQQQ, QEQEQQQ, QEQQEQQ, QEQQQEQ, QEQQQQE, QQEEQQQ, QQEQEQQ, QQEQQEQ, QQEQQQE, QQQEEQQ, QQQEQEQ, QQQEQQE, QQQQEEQ, QQQQEQE QQQQQQE, EQQQQQQ, QEQQQQQ, QQEQQQQ, QQQEQQQ, QQQQEQQ, QQQQQEQ, QQH, HQQ, QHQ, QQQH, HQQQ, QHQQ, QQHQ, QQQQH, HQQQQ, QHQQQ, QQHQQ, QQQHQ, QQQHH,

HHQQQ, HQHQQ, HQQHQ, HQQQH, QHHQQ, QHQHQ, QHQQH, QQHHQ, QQHQH, QQQQQH, HQQQQQ, QHQQQQ, QQHQQQ, QQQHQQ, QQQQHQ, QQQQHH, HHQQQQ, HQHQQQ, HQQHQQ, HQQQHQ, HQQQQH, QHHQQQ, QHQHQQ, QHQQHQ, QHQQQH, QQHHQQ, QQHQHQ, QQHQQH, QQQHHQ, QQQHQH, QQQQHHH, HHHQQQQ, HQHHQQQ, HQHQHQQ, HQHQQHQ, HQHQQQH, HQQHHQQ, HQQHQHQ, HQQHQQH, HQQQHQH, HQQQHHQ, HQQQQHH, HHQHQQQ, HHQQHQQ, HHQQQHQ, HHQQQQH, QHHHQQQ, QHHQHQQ, QHHQQHQ, QHHQQQH, QHQHHQQ, QHQQHHQ, QHQQQHH, QHQHQHQ, QHQHQQH, QHQQHQH, QQHHHQQ, QQHHQHQ, QQHHQQH, QQHQHHQ, QQHQHQH, QQHQQHH, QQQHHHQ, QQQHHQH, QQQHQHH, QQQQQHH, HHQQQQQ, HQHQQQQ, HQQHQQQ, HQQQHQQ, HQQQQHQ, HQQQQQH, QHHQQQQ, QHQHQQQ, QHQQHQQ, QHQQQHQ, QHQQQQH, QQHHQQQ, QQHQHQQ, QQHQQHQ, QQHQQQH, QQQHHQQ, QQQHQHQ, QQQHQQH, QQQQHHQ, QQQQHQH QQQQQQH, HQQQQQQ, QHQQQQQ, QQHQQQQ, QQQHQQQ, QQQQHQQ, QQQQQHQ, QQN, NQQ, QNQ, QQQN, NQQQ, QNQQ, QQNQ, QQQQN, NQQQQ, QNQQQ, QQNQQ, QQQNQ, QQQNN, NNQQQ, NQNQQ, NQQNQ, NQQQN, QNNQQ, QNQNQ, QNQQN, QQNNQ, QQNQN, QQQQQN, NQQQQQ, QNQQQQ, QQNQQQ, QQQNQQ, QQQQNQ, QQQQNN, NNQQQQ, NQNQQQ, NQQNQQ, NQQQNQ, NQQQQN, QNNQQQ, QNQNQQ, QNQQNQ, QNQQQN, QQNNQQ, QQNQNQ, QQNQQN, QQQNNQ, QQQNQN, QQQQNNN, NNNQQQQ, NQNNQQQ, NQNQNQQ, NQNQQNQ, NQNQQQN, NQQNNQQ, NQQNQNQ, NQQNQQN, NQQQNQN, NQQQNNQ, NQQQQNN, NNQNQQQ, NNQQNQQ, NNQQQNQ, NNQQQQN, QNNNQQQ, QNNQNQQ, QNNQQNQ, QNNQQQN, QNQNNQQ, QNQQNNQ, QNQQQNN, QNQNQNQ, QNQNQQN, QNQQNQN, QQNNNQQ, QQNNQNQ, QQNNQQN, QQNQNNQ, QQNQNQN, QQNQQNN, QQQNNNQ, QQQNNQN, QQQNQNN, QQQQQNN, NNQQQQQ, NQNQQQQ, NQQNQQQ, NQQQNQQ, NQQQQNQ, NQQQQQN, QNNQQQQ, QNQNQQQ, QNQQNQQ, QNQQQNQ, QNQQQQN, QQNNQQQ, QQNQNQQ, QQNQQNQ, QQNQQQN, QQQNNQQ, QQQNQNQ, QQQNQQN, QQQQNQQ, QQQQQNQ, QQD, DQQ, QDQ, QQQD, DQQQ, QDQQ, QQDQ, QQQQD, DQQQQ, QDQQQ, QQDQQ, QQQDQ, QQQDD, DDQQQ, DQDQQ, DQQDQ, DQQQD, QDDQQ, QDQDQ, QDQQD, QQDDQ,

QQDQD, QQQQQD, DQQQQQ, QDQQQQ, QQDQQQ, QQQDQQ, QQQQDQ, QQQQDD, DDQQQQ, DQDQQQ, DQQDQQ, DQQQDQ, DQQQQD, QDDQQQ, QDQDQQ, QDQQDQ, QDQQQD, QQDDQQ, QQDQDQ, QQDQQD, QQQDDQ, QQQDQD, QQQQDDD, DDDQQQQ, DQDDQQQ, DQDQDQQ, DQDQQDQ, DQDQQQD, DQQDDQQ, DQQDQDQ, DQQDQQD, DQQQDQD, DQQQDDQ, DQQQQDD, DDQDQQQ, DDQQDQQ, DDQQQDQ, DDQQQQD, QDDDQQQ, QDDQDQQ, QDDQQDQ, QDDQQQD, QDQDDQQ, QDQQDDQ, QDQQQDD, QDQDQDQ, QDQDQQD, QDQQDQD, QQDDDQQ, QQDDQDQ, QQDDQQD, QQDQDDQ, QQDQDQD, QQDQQDD, QQQDDDQ, QQQDDQD, QQQDQDD, QQQQQDD, DDQQQQQ, DQDQQQQ, DQQDQQQ, DQQQDQQ, DQQQQDQ, DQQQQQD, QDDQQQQ, QDQDQQQ, QDQQDQQ, QDQQQDQ, QDQQQQD, QQDDQQQQ, QQDQDQQ, QQDQQDQ, QQDQQQD, QQQDDQQ, QQQDQDQ, QQQDQQD, QQQQDDQ, QQQQDQD QQQQQQD, DQQQQQQ, QDQQQQQ, QQDQQQQ, QQQDQQQ, QQQQDQQ, and QQQQQDQ.

TABLE 4

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        10          20          30          40          50          60
MFLQNLFLGF LAVVCANATP LGPASSLPQS FLLKCLEQVR KIQGDGAALQ EKLCATYKLC
        70          80          90         100         110         120
HPEELVLLGH SLGIPWAPLS SCPSQALQLA GCLSQLHSGL FLYQGLLQAL EGISPELGPT
       130         140         150         160         170         180
LDTLQLDVAD FATTIWQQME ELGMAPALQP TQGAMPAFAS AFQRRAGGVL VASHLQSFLE
       190         200         210         220         230         240
VSYRVLRHLA QPNNTNNTNN TNNTNNTNNT NNTNNTNNTN NTNNTNNTNN TNNTNNTNNT
       250         260         270         280         290         300
NNTNNTNNTN NTNNTNNTNN TNNTNNTNNT NNTNNTNNTN NTNNTNNTNN TNNTNNTNNT
       310         320         330         340         350         360
NNTNNTNNTN NTNNTNNTNN TNNTNNTNNT NNTNNTNNTN NTNNTNN*.. ..........
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TABLE 4 (Continued)

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        10          20          30          40          50          60
atgttcttgc aaaatttatt ccttggcttt ttggccgttg tttgcgcaaa cgcgACTCCG
        70          80          90         100         110         120
CTGGGTCCAG CTAGCTCCCT GCCCCAGAGC TTCCTGCTCA AGTGCTTAGA GCAAGTGAGG
       130         140         150         160         170         180
AAGATCCAGG GCGATGGCGC AGCGCTCCAG GAGAAGCTGT GTGCCACCTA CAAGCTGTGC
       190         200         210         220         230         240
CACCCCGAGG AGCTGGTGCT GCTCGGACAC TCTCTGGGCA TCCCCTGGGC TCCCCTGAGC
       250         260         270         280         290         300
AGCTGCCCCA GCCAGGCCCT GCAGCTGGCA GGCTGCTTGA GCCAACTCCA TAGCGGCCTT
       310         320         330         340         350         360
TTCCTCTACC AGGGGCTCCT GCAGGCCCTG GAAGGGATCT CCCCCGAGTT GGGTCCCACC
       370         380         390         400         410         420
TTGGACACAC TGCAGCTGGA CGTCGCCGAC TTTGCCACCA CCATCTGGCA GCAGATGGAA
       430         440         450         460         470         480
GAACTGGGAA TGGCCCCTGC CCTGCAGCCG ACCCAGGGTG CCATGCCGGC CTTCGCCTCT
       490         500         510         520         530         540
GCTTTCCAGC GCCGGGCAGG AGGGGTCCTA GTTGCCTCCC ATCTGCAGAG CTTCCTGGAG
       550         560         570         580         590         600
GTGTCGTACC GCGTTCTACG CCACCTTGCC CAGCCTAACA ACACCAACAA TACCAACAAT
       610         620         630         640         650         660
ACAAACAACA CCAACAATAC CAACAATACA AACAACACCA ACAATACCAA CAATACAAAC
       670         680         690         700         710         720
AACACCAACA ATACCAACAA TACAAACAAC ACCAACAATA CCAACAATAC AAACAACACC
       730         740         750         760         770         780
AACAATACCA ACAATACAAA CAACACCAAC AATACCAACA ATACAAACAA CACCAATAAT
       790         800         810         820         830         840
ACCAACAATA CAAACAACAC CAATAATACC AACAATACAA ACAACACCAA TAATACCAAC
       850         860         870         880         890         900
AATACAAACA ACACCAATAA TACCAACAAT ACAAACAACA CCAATAATAC CAACAATACA
       910         920         930         940         950         960
AACAACACCA ATAATACCAA CAATACAAAC AACACCAATA ATACCAACAA TACAAACAAC
       970         980         990        1000        1010        1020
ACCAATAATA CCAACAATAC AAACAACACC AATAATACCA ACAATACAAA CAACACCAAT
      1030        1040        1050        1060        1070        1080
AATACCAACA ATACAAACAA CTAG..... ..........  ..........  ..........
```

TABLE 5

EPO

Homo sapiens erythropoietin (EPO), mRNA.

ACCESSION NM_000799

VERSION NM_000799.2 GI:62240996

MGVHECPAWLWLLLSLLSLPLGLPVLGAPPRLICDSRVLERYLL
EAKEAENITTGCAEHCSLNENITVPDTKVNFYAWKRMEVGQQAV

EVWQGLALLSEAVLRGQALLVNSSQPWEPLQLHVDKAVSGLRSL

TTLLRALGAQKEAISPPDAASAAPLRTITADTFRKLFRVYSNFL

RGKLKLYTGEACRTGDR

1 cccggagccg gaccggggcc accgcgcccg ctctgctccg acaccgcgcc ccctggacag

61 ccgccctctc ctccaggccc gtggggctgg ccctgcaccg ccgagcttcc cgggatgagg

121 gccccggtg tggtcacccg gcgcgcccca ggtcgctgag ggaccccggc caggcgcgga

181 gatgggggtg cacgaatgtc ctgcctggct gtggcttctc ctgtccctgc tgtcgctccc

241 tctgggcctc ccagtcctgg gcgccccacc acgcctcatc tgtgacagcc gagtcctgga

301 gaggtacctc ttggaggcca aggaggccga gaatatcacg acgggctgtg ctgaacactg

361 cagcttgaat gagaatatca ctgtcccaga caccaaagtt aatttctatg cctggaagag

421 gatggaggtc gggcagcagg ccgtagaagt ctggcagggc ctggccctgc tgtcggaagc

481 tgtcctgcgg ggccaggccc tgttggtcaa ctcttcccag ccgtgggagc ccctgcagct

541 gcatgtggat aaagccgtca gtggccttcg cagcctcacc actctgcttc gggctctggg

601 agcccagaag gaagccatct cccctccaga tgcggcctca gctgctccac tccgaacaat

661 cactgctgac actttccgca aactcttccg agtctactcc aatttcctcc ggggaaagct

721 gaagctgtac acaggggagg cctgcaggac aggggacaga tgaccaggtg tgtccacctg

781 ggcatatcca ccacctccct caccaacatt gcttgtgcca caccctcccc cgccactcct

841 gaaccccgtc gaggggctct cagctcagcg ccagcctgtc ccatggacac tccagtgcca

901 gcaatgacat ctcaggggcc agaggaactg tccagagagc aactctgaga tctaaggatg

961 tcacagggcc aacttgaggg cccagagcag gaagcattca gagagcagct ttaaactcag

1021 ggacagagcc atgctgggaa gacgcctgag ctcactcggc accctgcaaa atttgatgcc

1081 aggacacgct ttggaggcga tttacctgtt ttcgcaccta ccatcaggga caggatgacc

1141 tggagaactt aggtggcaag ctgtgacttc tccaggtctc acgggcatgg gcactccctt

1201 ggtggcaaga gccccttga caccggggtg gtgggaacca tgaagacagg atgggggctg

1261 gcctctggct ctcatggggt ccaagttttg tgtattcttc aacctcattg acaagaactg

1321 aaaccaccaa aaaaaaaaaa

MCSF

Homo sapiens colony stimulating factor 1 (macrophage) (CSF1),

transcript variant 4, mRNA.

ACCESSION NM_172212

VERSION NM_172212.1 GI:27262666

MTAPGAAGRCPPTTWLGSLLLLVCLLASRSITEEVSEYCSHMIG

SGHLQSLQRLIDSQMETSCQITFEFVDQEQLKDPVCYLKKAFLLVQDIMEDTMRFRDN

TPNAIAIVQLQELSLRLKSCFTKDYEEHDKACVRTFYETPLQLLEKVKNVFNETKNLL

DKDWNIFSKNCNNSFAECSSQDVVTKPDCNCLYPKAIPSSDPASVSPHQPLAPSMAPV

AGLTWEDSEGTEGSSLLPGEQPLHTVDPGSAKQRPPRSTCQSFEPPETPVVKDSTIGG

SPQPRPSVGAFNPGMEDILDSAMGTNWVPEEASGEASEIPVPQGTELSPSRPGGGSMQ

TEPARPSNFLSASSPLPASAKGQQPADVTGTALPRVGPVRPTGQDWNHTPQKTDHPSA

LLRDPPEPGSPRISSLRPQGLSNPSTLSAQPQLSRSHSSGSVLPLGELEGRRSTRDRR

SPAEPEGGPASEGAARPLPRFNSVPLTDTGHERQSEGSSSPQLQESVFHLLVPSVILV

LLAVGGLLFYRWRRRSHQEPQRADSPLEQPEGSPLTQDDRQVELPV

1 gagggctggc cagtgaggct cggcccgggg aaagtgaaag tttgcctggg tcctctcggc

61 gccagagccg ctctccgcat cccaggacag cggtgcggcc ctcggccggg gcgcccactc

121 cgcagcagcc agcgagcgag cgagcgagcg agggcggccg acgcgcccgg ccgggaccca

181 gctgcccgta tgaccgcgcc gggcgccgcc gggcgctgcc ctcccacgac atggctgggc

241 tccctgctgt tgttggtctg tctcctggcg agcaggagta tcaccgagga ggtgtcggag

301 tactgtagcc acatgattgg gagtggacac ctgcagtctc tgcagcggct gattgacagt

361 cagatggaga cctcgtgcca aattacattt gagtttgtag accaggaaca gttgaaagat

421 ccagtgtgct accttaagaa ggcatttctc ctggtacaag acataatgga ggacaccatg

481 cgcttcagag ataacacccc caatgccatc gccattgtgc agctgcagga actctctttg

541 aggctgaaga gctgcttcac caaggattat gaagagcatg acaaggcctg cgtccgaact

601 ttctatgaga cacctctcca gttgctggag aaggtcaaga atgtctttaa tgaaacaaag

661 aatctccttg acaaggactg gaatattttc agcaagaact gcaacaacag ctttgctgaa

721 tgctccagcc aagatgtggt gaccaagcct gattgcaact gcctgtaccc caaagccatc

781 cctagcagtg acccggcctc tgtctcccct catcagcccc tcgccccctc catggcccct

841 gtggctggct tgacctggga ggactctgag ggaactgagg gcagctccct cttgcctggt

901 gagcagcccc tgcacacagt ggatccaggc agtgccaagc agcggccacc caggagcacc

961 tgccagagct ttgagccgcc agagacccca gttgtcaagg acagcaccat cggtggctca

1021 ccacagcctc gcccctctgt cggggccttc aaccccggga tggaggatat tcttgactct

1081 gcaatgggca ctaattgggt cccagaagaa gcctctggag aggccagtga gattcccgta

1141 ccccaaggga cagagctttc cccctccagg ccaggagggg gcagcatgca gacagagccc

1201 gccagaccca gcaacttcct ctcagcatct tctccactcc ctgcatcagc aaagggccaa

1261 cagccggcag atgtaactgg tacagccttg cccagggtgg gccccgtgag gcccactggc

1321 caggactgga atcacacccc ccagaagaca gaccatccat ctgccctgct cagagacccc

1381 ccggagccag gctctcccag gatctcatca ctgcgccccc agggcctcag caacccctcc

1441 accctctctg ctcagccaca gctttccaga agccactcct cgggcagcgt gctgcccctt

1501 ggggagctgg agggcaggag gagcaccagg gatcggagga gccccgcaga gccagaagga

1561 ggaccagcaa gtgaaggggc agccaggccc ctgccccgtt ttaactccgt tcctttgact

1621 gacacaggcc atgagaggca gtccgaggga tcctccagcc cgcagctcca ggagtctgtc

1681 ttccacctgc tggtgcccag tgtcatcctg gtcttgctgg ccgtcggagg cctcttgttc

1741 tacaggtgga ggcggcggag ccatcaagag cctcagagag cggattctcc cttggagcaa

1801 ccagagggca gccccctgac tcaggatgac agacaggtgg aactgccagt gtagagggaa

1861 ttctaagacc cctcaccatc ctggacacac tcgtttgtca atgtccctct gaaaatgtga

1921 cgcccagccc cggacacagt actccagatg ttgtctgacc agctcagaga gagtacagtg

1981 ggactgttac cttccttgat atggacagta ttcttctatt tgtgcagatt aagattgcat

2041 tagtttttt cttaacaact gcatcatact gttgtcatat gttgagcctg tggttctata

2101 aaacccctag ttccatttcc cataaacttc tgtcaagcca gaccatctct accctgtact

2161 tggacaactt aacttttta accaaagtgc agtttatgtt caccttgtt aaagccacct

2221 ttgtggtttc tgcccatcac ctgaacctac tgaagttgtg tgaaatccta attctgtcat

2281 ctccgtagcc ctcccagttg tgcctcctgc acattgatga gtgcctgctg ttgtctttgc

2341 ccatgttgtt gatgtagctg tgaccctatt gttcctcacc cctgcccccc gccaacccca

2401 gctggcccac ctcttccccc tcccacccaa gcccacagcc agcccatcag gaagccttcc

2461 tggcttctcc acaaccttct gactgtcttt tcagtcatgc cccctgctct tttgtatttg

2521 gctaatagta tatcaatttg cactt

Homo sapiens colony stimulating factor 1 (macrophage) (CSF1),

transcript variant 3, mRNA.

ACCESSION NM_172211

VERSION NM_172211.1 GI:27262664

MTAPGAAGRCPPTTWLGSLLLLVCLLASRSITEEVSEYCSHMIG

SGHLQSLQRLIDSQMETSCQITFEFVDQEQLKDPVCYLKKAFLLVQDIMEDTMRFRDN

TPNAIAIVQLQELSLRLKSCFTKDYEEHDKACVRTFYETPLQLLEKVKNVFNETKNLL

DKDWNIFSKNCNNSFAECSSQGHERQSEGSSSPQLQESVFHLLVPSVILVLLAVGGLL

FYRWRRRSHQEPQRADSPLEQPEGSPLTQDDRQVELPV

1 gagggctggc cagtgaggct cggcccgggg aaagtgaaag tttgcctggg tcctctcggc

61 gccagagccg ctctccgcat cccaggacag cggtgcggcc ctcggccggg gcgcccactc

121 cgcagcagcc agcgagcgag cgagcgagcg agggcggccg acgcgcccgg ccgggaccca

181 gctgcccgta tgaccgcgcc gggcgccgcc gggcgctgcc ctcccacgac atggctgggc

241 tccctgctgt tgttggtctg tctcctggcg agcaggagta tcaccgagga ggtgtcggag

301 tactgtagcc acatgattgg gagtggacac ctgcagtctc tgcagcggct gattgacagt

361 cagatggaga cctcgtgcca aattacattt gagtttgtag accaggaaca gttgaaagat

421 ccagtgtgct accttaagaa ggcatttctc ctggtacaag acataatgga ggacaccatg

481 cgcttcagag ataacacccc caatgccatc gccattgtgc agctgcagga actctctttg

541 aggctgaaga gctgcttcac caaggattat gaagagcatg acaaggcctg cgtccgaact

601 ttctatgaga cacctctcca gttgctggag aaggtcaaga atgtctttaa tgaaacaaag

661 aatctccttg acaaggactg gaatattttc agcaagaact gcaacaacag ctttgctgaa

721 tgctccagcc aaggccatga gaggcagtcc gagggatcct ccagcccgca gctccaggag

781 tctgtcttcc acctgctggt gcccagtgtc atcctggtct tgctggccgt cggaggcctc

841 ttgttctaca ggtggaggcg gcggagccat caagagcctc agagagcgga ttctcccttg

901 gagcaaccag agggcagccc cctgactcag gatgacagac aggtggaact gccagtgtag

961 agggaattct aagctggacg cacagaacag tctctccgtg ggaggagaca ttatggggcg

1021 tccaccacca cccctccctg gccatcctcc tggaatgtgg tctgccctcc accagagctc

1081 ctgcctgcca ggactggacc agagcagcca ggctggggcc cctctgtctc aacccgcaga

1141 cccttgactg aatgagagag gccagaggat gctccccatg ctgccactat ttattgtgag

1201 ccctggaggc tcccatgtgc ttgaggaagg ctggtgagcc cggctcagga ccctcttccc

1261 tcaggggctg caccctcctc tcactccctt ccatgccgga acccaggcca gggacccacc

1321 ggcctgtggt ttgtgggaaa gcagggtgga cgctgaggag tgaaagaacc ctgcacccag

1381 agggcctgcc tggtgccaag gtatcccagc ctggacaggc atggacctgt ctccagagag

1441 aggagcctga agttcgtggg gcgggacagc gtcggcctga tttcccgtaa aggtgtgcag

1501 cctgagagac gggaagagga ggcctctgga cctgctggtc tgcactgaca gcctgaaggg

1561 tctacaccct cggctcacct aagtgccctg tgctggttgc caggcgcaga ggggaggcca

1621 gccctgccct caggacctgc ctgacctgcc agtgatgcca agaggggat caagcactgg

1681 cctctgcccc tcctccttcc agcacctgcc agagcttctc caggaggcca agcagaggct

1741 cccctcatga aggaagccat tgcactgtga acactgtacc tgcctgctga acagcctgcc

1801 cccgtccatc catgagccag catccgtccg tcctccactc tccagcctct cccca

Homo sapiens colony stimulating factor 1 (macrophage) (CSF1),

transcript variant 2, mRNA.

ACCESSION NM_172210

VERSION NM_172210.1 GI:27262662

MTAPGAAGRCPPTTWLGSLLLLVCLLASRSITEEVSEYCSHMIG

SGHLQSLQRLIDSQMETSCQITFEFVDQEQLKDPVCYLKKAFLLVQDIMEDTMRFRDN

TPNAIAIVQLQELSLRLKSCFTKDYEEHDKACVRTFYETPLQLLEKVKNVFNETKNLL

DKDWNIFSKNCNNSFAECSSQDVVTKPDCNCLYPKAIPSSDPASVSPHQPLAPSMAPV

AGLTWEDSEGTEGSSLLPGEQPLHTVDPGSAKQRPPRSTCQSFEPPETPVVKDSTIGG

SPQPRPSVGAFNPGMEDILDSAMGTNWVPEEASGEASEIPVPQGTELSPSRPGGGSMQ

TEPARPSNFLSASSPLPASAKGQQPADVTGHERQSEGSSSPQLQESVFHLLVPSVILV

LLAVGGLLFYRWRRRSHQEPQRADSPLEQPEGSPLTQDDRQVELPV

1 gagggctggc cagtgaggct cggcccgggg aaagtgaaag tttgcctggg tcctctcggc

61 gccagagccg ctctccgcat cccaggacag cggtgcggcc ctcggccggg gcgcccactc

121 cgcagcagcc agcgagcgag cgagcgagcg agggcggccg acgcgcccgg ccgggaccca

181 gctgcccgta tgaccgcgcc gggcgccgcc gggcgctgcc ctcccacgac atggctgggc

241 tccctgctgt tgttggtctg tctcctggcg agcaggagta tcaccgagga ggtgtcggag

301 tactgtagcc acatgattgg gagtggacac ctgcagtctc tgcagcggct gattgacagt

361 cagatggaga cctcgtgcca aattacattt gagtttgtag accaggaaca gttgaaagat

421 ccagtgtgct accttaagaa ggcatttctc ctggtacaag acataatgga ggacaccatg

481 cgcttcagag ataacacccc caatgccatc gccattgtgc agctgcagga actctctttg

541 aggctgaaga gctgcttcac caaggattat gaagagcatg acaaggcctg cgtccgaact

601 ttctatgaga cacctctcca gttgctggag aaggtcaaga atgtctttaa tgaaacaaag

661 aatctccttg acaaggactg gaatattttc agcaagaact gcaacaacag ctttgctgaa

721 tgctccagcc aagatgtggt gaccaagcct gattgcaact gcctgtaccc caaagccatc

781 cctagcagtg acccggcctc tgtctccccc catcagcccc tcgccccctc catggccccc

841 gtggctggct tgacctggga ggactctgag ggaactgagg gcagctccct cttgcctggt

901 gagcagcccc tgcacacagt ggatccaggc agtgccaagc agcggccacc caggagcacc

961 tgccagagct ttgagccgcc agagacccca gttgtcaagg acagcaccat cggtggctca

1021 ccacagcctc gcccctctgt cggggccttc aaccccggga tggaggatat tcttgactct

1081 gcaatgggca ctaattgggt cccagaagaa gcctctggag aggccagtga gattcccgta

1141 ccccaaggga cagagctttc cccctccagg ccaggagggg gcagcatgca gacagagccc

1201 gccagaccca gcaacttcct ctcagcatct tctccactcc ctgcatcagc aaagggccaa

1261 cagccggcag atgtaactgg ccatgagagg cagtccgagg gatcctccag cccgcagctc

1321 caggagtctg tcttccacct gctggtgccc agtgtcatcc tggtcttgct ggccgtcgga

1381 ggcctcttgt tctacaggtg gaggcggcgg agccatcaag agcctcagag agcggattct

1441 cccttggagc aaccagaggg cagccccctg actcaggatg acagacaggt ggaactgcca

1501 gtgtagaggg aattctaag

Homo sapiens colony stimulating factor 1 (macrophage) (CSF1),

transcript variant 1, mRNA.

ACCESSION NM_000757

VERSION NM_000757.3 GI:27262660

MTAPGAAGRCPPTTWLGSLLLLVCLLASRSITEEVSEYCSHMIG

SGHLQSLQRLIDSQMETSCQITFEFVDQEQLKDPVCYLKKAFLLVQDIMEDTMRFRDN

TPNAIAIVQLQELSLRLKSCFTKDYEEHDKACVRTFYETPLQLLEKVKNVFNETKNLL

DKDWNIFSKNCNNSFAECSSQDVVTKPDCNCLYPKAIPSSDPASVSPHQPLAPSMAPV

AGLTWEDSEGTEGSSLLPGEQPLHTVDPGSAKQRPPRSTCQSFEPPETPVVKDSTIGG

SPQPRPSVGAFNPGMEDILDSAMGTNWVPEEASGEASEIPVPQGTELSPSRPGGGSMQ

TEPARPSNFLSASSPLPASAKGQQPADVTGTALPRVGPVRPTGQDWNHTPQKTDHPSA

LLRDPPEPGSPRISSLRPQGLSNPSTLSAQPQLSRSHSSGSVLPLGELEGRRSTRDRR

SPAEPEGGPASEGAARPLPRFNSVPLTDTGHERQSEGSSSPQLQESVFHLLVPSVILV

LLAVGGLLFYRWRRRSHQEPQRADSPLEQPEGSPLTQDDRQVELPV

1 gagggctggc cagtgaggct cggcccgggg aaagtgaaag tttgcctggg tcctctcggc

61 gccagagccg ctctccgcat cccaggacag cggtgcggcc ctcggccggg gcgcccactc

121 cgcagcagcc agcgagcgag cgagcgagcg agggcggccg acgcgcccgg ccgggaccca

181 gctgcccgta tgaccgcgcc gggcgccgcc gggcgctgcc ctcccacgac atggctgggc

241 tccctgctgt tgttggtctg tctcctggcg agcaggagta tcaccgagga ggtgtcggag

301 tactgtagcc acatgattgg gagtggacac ctgcagtctc tgcagcggct gattgacagt

361 cagatggaga cctcgtgcca aattacattt gagtttgtag accaggaaca gttgaaagat

421 ccagtgtgct accttaagaa ggcatttctc ctggtacaag acataatgga ggacaccatg

481 cgcttcagag ataacacccc caatgccatc gccattgtgc agctgcagga actctctttg

541 aggctgaaga gctgcttcac caaggattat gaagagcatg acaaggcctg cgtccgaact

601 ttctatgaga cacctctcca gttgctggag aaggtcaaga atgtctttaa tgaaacaaag

661 aatctccttg acaaggactg gaatattttc agcaagaact gcaacaacag ctttgctgaa

721 tgctccagcc aagatgtggt gaccaagcct gattgcaact gcctgtaccc caaagccatc

781 cctagcagtg acccggcctc tgtctccccc catcagcccc tcgccccctc catggccccc

841 gtggctggct tgacctggga ggactctgag ggaactgagg gcagctcccc cttgcctggt

901 gagcagcccc tgcacacagt ggatccaggc agtgccaagc agcggccacc caggagcacc

961 tgccagagct ttgagccgcc agagacccca gttgtcaagg acagcaccat cggtggctca

1021 ccacagcctc gcccctctgt cggggccttc aaccccggga tggaggatat tcttgactct

1081 gcaatgggca ctaattgggt cccagaagaa gcctctggag aggccagtga gattcccgta

1141 ccccaaggga cagagctttc cccctccagg ccaggagggg gcagcatgca gacagagccc

1201 gccagaccca gcaacttcct ctcagcatct tctccactcc ctgcatcagc aaagggccaa

1261 cagccggcag atgtaactgg tacagccttg cccagggtgg gccccgtgag gcccactggc

1321 caggactgga atcacacccc ccagaagaca gaccatccat ctgccctgct cagagacccc

1381 ccggagccag gctctcccag gatctcatca ctgcgccccc agggcctcag caacccctcc

1441 accctctctg ctcagccaca gctttccaga agccactcct cgggcagcgt gctgcccctt

1501 ggggagctgg agggcaggag gagcaccagg gatcggagga gccccgcaga gccagaagga

1561 ggaccagcaa gtgaaggggc agccaggccc ctgccccgtt ttaactccgt tcctttgact

1621 gacacaggcc atgagaggca gtccgaggga tcctccagcc cgcagctcca ggagtctgtc

1681 ttccacctgc tggtgcccag tgtcatcctg gtcttgctgg ccgtcggagg cctcttgttc

1741 tacaggtgga ggcggcggag ccatcaagag cctcagagag cggattctcc cttggagcaa

1801 ccagagggca gccccctgac tcaggatgac agacaggtgg aactgccagt gtagagggaa

1861 ttctaagctg gacgcacaga acagtctctc cgtgggagga gacattatgg ggcgtccacc

1921 accacccctc cctggccatc ctcctggaat gtggtctgcc ctccaccaga gctcctgcct

1981 gccaggactg gaccagagca gccaggctgg ggcccctctg tctcaacccg cagacccttg

2041 actgaatgag agaggccaga ggatgctccc catgctgcca ctatttattg tgagccctgg

2101 aggctcccat gtgcttgagg aaggctggtg agcccggctc aggaccctct tccctcaggg

2161 gctgcaccct cctctcactc ccttccatgc cggaacccag gccagggacc caccggcctg

2221 tggtttgtgg gaaagcaggg tggacgctga ggagtgaaag aaccctgcac ccagagggcc

2281 tgcctggtgc caaggtatcc cagcctggac aggcatggac ctgtctccag agagaggagc

2341 ctgaagttcg tggggcggga cagcgtcggc ctgatttccc gtaaaggtgt gcagcctgag

2401 agacgggaag aggaggcctc tggacctgct ggtctgcact gacagcctga agggtctaca

2461 ccctcggctc acctaagtgc cctgtgctgg ttgccaggcg cagaggggag gccagccctg

2521 ccctcaggac ctgcctgacc tgccagtgat gccaagaggg ggatcaagca ctggcctctg

2581 cccctcctcc ttccagcacc tgccagagct tctccaggag gccaagcaga ggctcccctc

2641 atgaaggaag ccattgcact gtgaacactg tacctgcctg ctgaacagcc tgccccccgtc

2701 catccatgag ccagcatccg tccgtcctcc actctccagc ctctcccca

GM-CSF

Homo sapiens colony stimulating factor 2 (granulocyte-macrophage)

(CSF2), mRNA.

ACCESSION NM_000758

VERSION NM_000758.2 GI:27437029

MWLQSLLLLGTVACSISAPARSPSPSTQPWEHVNAIQEARRLLN

LSRDTAAEMNETVEVISEMFDLQEPTCLQTRLELYKQGLRGSLT

KLKGPLTMMASHYKQHCPPTPETSCATQIITFESFKENLKDFLL

VIPFDCWEPVQE

1 acacagagag aaaggctaaa gttctctgga ggatgtggct gcagagcctg ctgctcttgg

61 gcactgtggc ctgcagcatc tctgcacccg cccgctcgcc cagccccagc acgcagccct

121 gggagcatgt gaatgccatc caggaggccc ggcgtctcct gaacctgagt agagacactg

181 ctgctgagat gaatgaaaca gtagaagtca tctcagaaat gtttgacctc caggagccga

241 cctgcctaca gacccgcctg gagctgtaca agcagggcct gcggggcagc ctcaccaagc

301 tcaagggccc cttgaccatg atggccagcc actacaagca gcactgccct ccaaccccgg

361 aaacttcctg tgcaacccag attatcacct ttgaaagttt caaagagaac ctgaaggact

421 ttctgcttgt catccccttt gactgctggg agccagtcca ggagtgagac cggccagatg

481 aggctggcca agccggggag ctgctctctc atgaaacaag agctagaaac tcaggatggt

541 catcttggag ggaccaaggg gtgggccaca gccatggtgg gagtggcctg gacctgccct

601 gggccacact gaccctgata caggcatggc agaagaatgg gaatatttta tactgacaga

661 aatcagtaat atttatatat ttatattttt aaaatattta tttatttatt tatttaagtt

721 catattccat atttattcaa gatgttttac cgtaataatt attattaaaa atatgcttct

781 a

TNF-ALPHA TYPE II RECEPTOR

Homo sapiens tumor necrosis factor (TNF superfamily, member 2)

(TNF), mRNA.

ACCESSION NM_000594

VERSION NM_000594.2 GI:25952110

MSTESMIRDVELAEEALPKKTGGPQGSRRCLFLSLFSFLIVAGA

TTLFCLLHFGVIGPQREEFPRDLSLISPLAQAVRSSSRTPSDKPVAHVVANPQAEGQL

QWLNRRANALLANGVELRDNQLVVPSEGLYLIYSQVLFKGQGCPSTHVLLTHTISRIA

VSYQTKVNLLSAIKSPCQRETPEGAEAKPWYEPIYLGGVFQLEKGDRLSAEINRPDYL

DFAESGQVYFGIIAL

1 ctccctcagc aaggacagca gaggaccagc taagagggag agaagcaact acagaccccc

61 cctgaaaaca accctcagac gccacatccc ctgacaagct gccaggcagg ttctcttcct

121 ctcacatact gacccacggc tccaccctct ctcccctgga aaggacacca tgagcactga

181 aagcatgatc cgggacgtgg agctggccga ggaggcgctc cccaagaaga caggggggcc

241 ccagggctcc aggcggtgct tgttcctcag cctcttctcc ttcctgatcg tggcaggcgc

301 caccacgctc ttctgcctgc tgcactttgg agtgatcggc ccccagaggg aagagttccc

361 cagggacctc tctctaatca gccctctggc ccaggcagtc agatcatctt ctcgaacccc

421 gagtgacaag cctgtagccc atgttgtagc aaaccctcaa gctgaggggc agctccagtg

481 gctgaaccgc cgggccaatg ccctcctggc caatggcgtg gagctgagag ataaccagct

541 ggtggtgcca tcagagggcc tgtacctcat ctactcccag gtcctcttca agggccaagg

601 ctgcccctcc acccatgtgc tcctcaccca caccatcagc cgcatcgccg tctcctacca

661 gaccaaggtc aacctcctct ctgccatcaa gagcccctgc cagagggaga ccccagaggg

721 ggctgaggcc aagccctggt atgagcccat ctatctggga ggggtcttcc agctggagaa

781 gggtgaccga ctcagcgctg agatcaatcg gcccgactat ctcgactttg ccgagtctgg

841 gcaggtctac tttgggatca ttgccctgtg aggaggacga acatccaacc ttcccaaacg

901 cctcccctgc cccaatccct ttattacccc ctccttcaga caccctcaac ctcttctggc

961 tcaaaaagag aattgggggc ttagggtcgg aacccaagct tagaacttta agcaacaaga

1021 ccaccacttc gaaacctggg attcaggaat gtgtggcctg cacagtgaag tgctggcaac

1081 cactaagaat tcaaactggg gcctccagaa ctcactgggg cctacagctt tgatccctga

1141 catctggaat ctggagacca gggagccttt ggttctggcc agaatgctgc aggacttgag

1201 aagacctcac ctagaaattg acacaagtgg accttaggcc ttcctctctc cagatgtttc

1261 cagacttcct tgagacacgg agcccagccc tccccatgga gccagctccc tctatttatg

1321 tttgcacttg tgattattta ttatttattt attatttatt tatttacaga tgaatgtatt

1381 tatttgggag accggggtat cctgggggac ccaatgtagg agctgccttg gctcagacat

1441 gttttccgtg aaaacggagc tgaacaatag gctgttccca tgtagccccc tggcctctgt

1501 gccttctttt gattatgttt tttaaaatat ttatctgatt aagttgtcta aacaatgctg

1561 atttggtgac caactgtcac tcattgctga gcctctgctc cccaggggag ttgtgtctgt

1621 aatcgcccta ctattcagtg gcgagaaata aagtttgctt agaaaagaa

DEFINITION Homo sapiens tumor necrosis factor receptor superfamily, member 1A

(TNFRSF1A), mRNA.

ACCESSION NM_001065

VERSION NM_001065.2 GI:23312372

MGLSTVPDLLLPLVLLELLVGIYPSGVIGLVPHLGDREKRDSVC

PQGKYIHPQNNSICCTKCHKGTYLYNDCPGPGQDTDCRECESGSFTASENHLRHCLSC

SKCRKEMGQVEISSCTVDRDTVCGCRKNQYRHYWSENLFQCFNCSLCLNGTVHLSCQE

KQNTVCTCHAGFFLRENECVSCSNCKKSLECTKLCLPQIENVKGTEDSGTTVLLPLVI

FFGLCLLSLLFIGLMYRYQRWKSKLYSIVCGKSTPEKEGELEGTTTKPLAPNPSFSPT

PGFTPTLGFSPVPSSTFTSSSTYTPGDCPNFAAPRREVAPPYQGADPILATALASDPI

PNPLQKWEDSAHKPQSLDTDDPATLYAVVENVPPLRWKEFVRRLGLSDHEIDRLELQN

GRCLREAQYSMLATWRRRTPRREATLELLGRVLRDMDLLGCLEDIEEALCGPAALPPA

PSLLR

1 gctgttgcaa cactgcctca ctcttcccct cccaccttct ctcccctcct ctctgcttta

61 attttctcag aattctctgg actgaggctc cagttctggc ctttggggtt caagatcact

121 gggaccaggc cgtgatctct atgcccgagt ctcaaccctc aactgtcacc ccaaggcact

181 tgggacgtcc tggacagacc gagtcccggg aagccccagc actgccgctg ccacactgcc

241 ctgagcccaa atgggggagt gagaggccat agctgtctgg catgggcctc tccaccgtgc

301 ctgacctgct gctgccactg gtgctcctgg agctgttggt gggaatatac ccctcagggg

361 ttattggact ggtccctcac ctaggggaca gggagaagag agatagtgtg tgtccccaag

421 gaaaatatat ccaccctcaa aataattcga tttgctgtac caagtgccac aaaggaacct

481 acttgtacaa tgactgtcca ggcccggggc aggatacgga ctgcagggag tgtgagagcg

541 gctccttcac cgcttcagaa aaccacctca gacactgcct cagctgctcc aaatgccgaa

601 aggaaatggg tcaggtggag atctcttctt gcacagtgga ccgggacacc gtgtgtggct

661 gcaggaagaa ccagtaccgg cattattgga gtgaaaacct tttccagtgc ttcaattgca

721 gcctctgcct caatgggacc gtgcacctct cctgccagga gaaacagaac accgtgtgca

781 cctgccatgc aggtttcttt ctaagagaaa acgagtgtgt ctcctgtagt aactgtaaga

841 aaagcctgga gtgcacgaag ttgtgcctac cccagattga gaatgttaag ggcactgagg

901 actcaggcac cacagtgctg ttgcccctgg tcattttctt tggtctttgc cttttatccc

961 tcctcttcat tggtttaatg tatcgctacc aacggtggaa gtccaagctc tactccattg

1021 tttgtgggaa atcgacacct gaaaaagagg gggagcttga aggaactact actaagcccc

1081 tggccccaaa cccaagcttc agtcccactc caggcttcac ccccaccctg ggcttcagtc

1141 ccgtgcccag ttccaccttc acctccagct ccacctatac ccccggtgac tgtcccaact

1201 ttgcggctcc ccgcagagag gtggcaccac cctatcaggg ggctgacccc atccttgcga

1261 cagccctcgc ctccgacccc atccccaacc cccttcagaa gtgggaggac agcgcccaca

1321 agccacagag cctagacact gatgaccccg cgacgctgta cgccgtggtg gagaacgtgc

1381 ccccgttgcg ctggaaggaa ttcgtgcggc gcctagggct gagcgaccac gagatcgatc

1441 ggctggagct gcagaacggg cgctgcctgc gcgaggcgca atacagcatg ctggcgacct

1501 ggaggcggcg cacgccgcgg cgcgaggcca cgctggagct gctgggacgc gtgctccgcg

1561 acatggacct gctgggctgc ctggaggaca tcgaggaggc gctttgcggc cccgccgccc

1621 tcccgcccgc gcccagtctt ctcagatgag gctgcgcccc tgcgggcagc tctaaggacc

1681 gtcctgcgag atcgccttcc aaccccactt ttttctggaa aggaggggtc ctgcaggggc

1741 aagcaggagc tagcagccgc ctacttggtg ctaacccctc gatgtacata gcttttctca

1801 gctgcctgcg cgccgccgac agtcagcgct gtgcgcgcgg agagaggtgc gccgtgggct

1861 caagagcctg agtgggtggt ttgcgaggat gagggacgct atgcctcatg cccgttttgg

1921 gtgtcctcac cagcaaggct gctcgggggc ccctggttcg tccctgagcc tttttcacag

1981 tgcataagca gttttttttg tttttgtttt gttttgtttt gtttttaaat caatcatgtt

2041 acactaatag aaacttggca ctcctgtgcc ctctgcctgg acaagcacat agcaagctga

2101 actgtcctaa ggcaggggcg agcacggaac aatggggcct tcagctggag ctgtggactt

2161 ttgtacatac actaaaattc tgaagttaaa gctctgctct tggaaaaaaa aaaaaaaaaa

2221 aaaaaaaaaa aaaaa

BETA INTERFERON

Homo sapiens interferon, beta 1, fibroblast (IFNB1), mRNA.

ACCESSION NM_002176

VERSION NM_002176.2 GI:50593016

MTNKCLLQIALLLCFSTTALSMSYNLLGFLQRSSNFQCQKLLWQ

LNGRLEYCLKDRMNFDIPEEIKQLQQFQKEDAALTIYEMLQNIFAIFRQDSSSTGWNE

TIVENLLANVYHQINHLKTVLEEKLEKEDFTRGKLMSSLHLKRYYGRILHYLKAKEYS

HCAWTIVRVEILRNFYFINRLTGYLRN

1 acattctaac tgcaaccttt cgaagccttt gctctggcac aacaggtagt aggcgacact

61 gttcgtgttg tcaacatgac caacaagtgt ctcctccaaa ttgctctcct gttgtgcttc

121 tccactacag ctctttccat gagctacaac ttgcttggat tcctacaaag aagcagcaat

181 tttcagtgtc agaagctcct gtggcaattg aatgggaggc ttgaatactg cctcaaggac

241 aggatgaact ttgacatccc tgaggagatt aagcagctgc agcagttcca gaaggaggac

301 gccgcattga ccatctatga gatgctccag aacatctttg ctattttcag acaagattca

361 tctagcactg gctggaatga gactattgtt gagaacctcc tggctaatgt ctatcatcag

421 ataaaccatc tgaagacagt cctggaagaa aaactggaga aagaagattt caccagggga

481 aaactcatga gcagtctgca cctgaaaaga tattatggga ggattctgca ttacctgaag

541 gccaaggagt acagtcactg tgcctggacc atagtcagag tggaaatcct aaggaacttt

601 tacttcatta acagacttac aggttacctc cgaaactgaa gatctcctag cctgtgcctc

661 tgggactgga caattgcttc aagcattctt caaccagcag atgctgttta agtgactgat

721 ggctaatgta ctgcatatga aaggacacta gaagattttg aaatttttat taaattatga

781 gttattttta tttatttaaa ttttattttg gaaaataaat tatttttggt gcaaaagtca

GAMMA INTERFERON

Homo sapiens interferon, gamma (IFNG), mRNA.

ACCESSION NM_000619

VERSION NM_000619.2 GI:56786137

MKYTSYILAFQLCIVLGSLGCYCQDPYVKEAENLKKYFNAGHSD

VADNGTLFLGILKNWKEESDRKIMQSQIVSFYFKLFKNFKDDQSIQKSVETIKEDMNV

KFFNSNKKKRDDFEKLTNYSVTDLNVQRKAIHELIQVMAELSPAAKTGKRKRSQMLFR

GRRASQ

1 cacattgttc tgatcatctg aagatcagct attagaagag aaagatcagt taagtccttt

61 ggacctgatc agcttgatac aagaactact gatttcaact tctttggctt aattctctcg

121 gaaacgatga aatatacaag ttatatcttg gcttttcagc tctgcatcgt tttgggttct

181 cttggctgtt actgccagga cccatatgta aaagaagcag aaaaccttaa gaaatatttt

241 aatgcaggtc attcagatgt agcggataat ggaactcttt tcttaggcat tttgaagaat

301 tggaaagagg agagtgacag aaaaataatg cagagccaaa ttgtctcctt ttacttcaaa

361 ctttttaaaa actttaaaga tgaccagagc atccaaaaga gtgtggagac catcaaggaa

421 gacatgaatg tcaagttttt caatagcaac aaaaagaaac gagatgactt cgaaaagctg

481 actaattatt cggtaactga cttgaatgtc caacgcaaag caatacatga actcatccaa

541 gtgatggctg aactgtcgcc agcagctaaa acagggaagc gaaaaaggag tcagatgctg

601 tttcgaggtc gaagagcatc ccagtaatgg ttgtcctgcc tgcaatattt gaattttaaa

661 tctaaatcta tttattaata tttaacatta tttatatggg gaatatattt ttagactcat

721 caatcaaata agtatttata atagcaactt ttgtgtaatg aaaatgaata tctattaata

781 tatgtattat ttataattcc tatatcctgt gactgtctca cttaatcctt tgttttctga

841 ctaattaggc aaggctatgt gattacaagg ctttatctca ggggccaact aggcagccaa

901 cctaagcaag atcccatggg ttgtgtgttt atttcacttg atgatacaat gaacacttat

961 aagtgaagtg atactatcca gttactgccg gtttgaaaat atgcctgcaa tctgagccag

1021 tgctttaatg gcatgtcaga cagaacttga atgtgtcagg tgaccctgat gaaaacatag

1081 catctcagga gatttcatgc ctggtgcttc caaatattgt tgacaactgt gactgtaccc

1141 aaatggaaag taactcattt gttaaaatta tcaatatcta atatatatga ataaagtgta

1201 agttcacaac aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa

HUMAN GROWTH HORMONE

Human growth hormone (somatotropin, GH1) gene, complete cds.

ACCESSION J00148 K00612

VERSION J00148.1 GI:183145

MATGSRTSLLLAFGLLCLPWLQEGSAFPTIPLSRLFDNASLRAH

RLHQLAFDTYQEFNPQTSLCFSESIPTPSNREETQQKSNLELLRISLLLIQSWLEPVQ

FLRSVFANSLVYGASDSNVYDLLKDLEEGIQTLMGRLEDGSPRTGQIFKQTYSKFDTN

SHNDDALLKNYGLLYCFRKDMDKVETFLRIVQCRSVEGSCGF

1 agggcaccca cgtgaccctt aaagagagga caagttgggt ggtattttct ggctgacact

61 ctgtgcacaa ccctcacaac actggttgac ggtgggaagg gaaagatgac aagccagggg

121 catgatccca gcatgtgtgg gaggagcttc taaattatcc attagcacaa gcccgtcagt

181 ggccccatgc ataaatgtac acagaaacag gtgggggcaa cagtgggaga gaaggggcca

241 gggtataaaa agggcccaca agagaccggc tcaaggatcc caaggcccaa ctccccgaac

301 cactcagggt cctgtggacg ctcacctagc tgcaatggct acaggtaagc gcccctaaaa

361 tccctttggg cacaatgtgt cctgagggga gaggcagcga cctgtagatg ggacgggggc

421 actaaccctc aggtttgggg cttctgaatg agtatcgcca tgtaagccca gtatggccaa

481 tctcagaaag ctcctggtcc ctggagggat ggagagagaa aaacaaacag ctcctggagc

541 agggagagtg ctggcctctt gctctccggc tccctctgtt gccctctggt ttctccccag

601 gctcccggac gtccctgctc ctggcttttg gcctgctctg cctgccctgg cttcaagagg

661 gcagtgcctt cccaaccatt cccttatcca ggctttttga caacgctagt ctccgcgccc

721 atcgtctgca ccagctggcc tttgacacct accaggagtt tgtaagctct tggggaatgg

781 gtgcgcatca ggggtggcag gaaggggtga ctttcccccg ctgggaaata agaggaggag

841 actaaggagc tcagggtttt tcccgaagcg aaaatgcagg cagatgagca cacgctgagt

901 gaggttccca gaaaagtaac aatgggagct ggtctccagc gtagaccttg gtgggcggtc

961 cttctcctag gaagaagcct atatcccaaa ggaacagaag tattcattcc tgcagaaccc

1021 ccagacctcc ctctgtttct cagagtctat tccgacaccc tccaacaggg aggaaacaca

1081 acagaaatcc gtgagtggat gccttgaccc caggcgggga tgggggagac ctgtagtcag

1141 agcccccggg cagcacaggc caatgcccgt ccttcccctg cagaacctag agctgctccg

1201 catctccctg ctgctcatcc agtcgtggct ggagcccgtg cagttcctca ggagtgtctt

1261 cgccaacagc ctggtgtacg gcgcctctga cagcaacgtc tatgacctcc taaaggacct

1321 agaggaaggc atccaaacgc tgatgggggt gggggtggcg ctaggggtcc ccaatcttgg

1381 agccccactg actttgagag ctgtgttaga gaaacactgc tgccctcttt ttagcagtcc

1441 aggccctgac ccaagagaac tcaccttatt cttcatttcc cctcgtgaat cctctagcct

1501 ttctctacac cctgaagggg agggaggaaa atgaatgaat gagaaaggga gggagcagta

1561 cccaagcgct tggcctctcc ttctcttcct tcactttgca gaggctggaa gatggcagcc

1621 cccggactgg gcagatcttc aagcagacct acagcaagtt cgacacaaac tcacacaacg

1681 atgacgcact actcaagaac tacgggctgc tctactgctt caggaaggac atggacaagg

1741 tcgagacatt cctgcgcatc gtgcagtgcc gctctgtgga gggcagctgt ggcttctagc

1801 tgcccgggtg gcatccctgt gacccctccc cagtgcctct cctggccttg gaagttgcca

1861 ctccagtgcc caccagcctt gtcctaataa aattaagttg catcattttg tctgactagg

1921 tgtcctctat aatattatgg ggtggagggg ggtggtttgg agca

COGULATION FACTORS

Homo sapiens coagulation factor VII (serum prothrombin conversion

accelerator) (F7), transcript variant 2, mRNA.

ACCESSION NM_019616

VERSION NM_019616.1 GI:10518502

MVSQALRLLCLLLGLQGCLAAVFVTQEEAHGVLHRRRRANAFLE

ELRPGSLERECKEEQCSFEEAREIFKDAERTKLFWISYSDGDQCASSPCQNGGSCKDQ

LQSYICFCLPAFEGRNCETHKDDQLICVNENGGCEQYCSDHTGTKRSCRCHEGYSLLA

DGVSCTPTVEYPCGKIPILEKRNASKPQGRIVGGKVCPKGECPWQVLLLVNGAQLCGG

TLINTIWVVSAAHCFDKIKNWRNLIAVLGEHDLSEHDGDEQSRRVAQVIIPSTYVPGT

TNHDIALLRLHQPVVLTDHVVPLCLPERTFSERTLAFVRFSLVSGWGQLLDRGATALE

LMVLNVPRLMTQDCLQQSRKVGDSPNITEYMFCAGYSDGSKDSCKGDSGGPHATHYRG

TWYLTGIVSWGQGCATVGHFGVYTRVSQYIEWLQKLMRSEPRPGVLLRAPFP

1 agtcccatgg ggaatgtcaa caggcagggg cagcactgca gagatttcat catggtctcc

61 caggccctca ggctcctctg ccttctgctt gggcttcagg gctgcctggc tgcagtcttc

121 gtaacccagg aggaagccca cggcgtcctg caccggcgcc ggcgcgccaa cgcgttcctg

181 gaggagctgc ggccgggctc cctggagagg gagtgcaagg aggagcagtg ctccttcgag

241 gaggcccggg agatcttcaa ggacgcggag aggacgaagc tgttctggat ttcttacagt

301 gatggggacc agtgtgcctc aagtccatgc cagaatgggg gctcctgcaa ggaccagctc

361 cagtcctata tctgcttctg cctccctgcc ttcgagggcc ggaactgtga gacgcacaag

421 gatgaccagc tgatctgtgt gaacgagaac ggcggctgtg agcagtactg cagtgaccac

481 acgggcacca agcgctcctg tcggtgccac gaggggtact ctctgctggc agacggggtg

541 tcctgcacac ccacagttga atatccatgt ggaaaaatac ctattctaga aaaaagaaat

601 gccagcaaac cccaaggccg aattgtgggg ggcaaggtgt gccccaaagg ggagtgtcca

661 tggcaggtcc tgttgttggt gaatggagct cagttgtgtg gggggaccct gatcaacacc

721 atctgggtgg tctccgcggc ccactgtttc gacaaaatca agaactggag gaacctgatc

781 gcggtgctgg gcgagcacga cctcagcgag cacgacgggg atgagcagag ccggcgggtg

841 gcgcaggtca tcatccccag cacgtacgtc ccgggcacca ccaaccacga catcgcgctg

901 ctccgcctgc accagcccgt ggtcctcact gaccatgtgg tgcccctctg cctgcccgaa

961 cggacgttct ctgagaggac gctggccttc gtgcgcttct cattggtcag cggctggggc

1021 cagctgctgg accgtggcgc cacggccctg gagctcatgg tgctcaacgt gccccggctg

1081 atgacccagg actgcctgca gcagtcacgg aaggtgggag actccccaaa tatcacggag

1141 tacatgttct gtgccggcta ctcggatggc agcaaggact cctgcaaggg ggacagtgga

1201 ggcccacatg ccacccacta ccggggcacg tggtacctga cgggcatcgt cagctggggc

1261 cagggctgcg caaccgtggg ccactttggg gtgtacacca gggtctccca gtacatcgag

1321 tggctgcaaa agctcatgcg ctcagagcca cgcccaggag tcctcctgcg agccccattt

1381 ccctagccca gcagccctgg cctgtggaga gaaagccaag gctgcgtcga actgtcctgg

1441 caccaaatcc catatattct tctgcagtta atggggtaga ggagggcatg ggagggaggg

1501 agaggtgggg agggagacag agacagaaac agagagagac agagacagag agagactgag

1561 ggagagactc tgaggacatg gagagagact caaagagact ccaagattca aagagactaa

1621 tagagacaca gagatggaat agaaaagatg agaggcagag gcagacaggc gctggacaga

1681 ggggcagggg agtgccaagg ttgtcctgga ggcagacagc ccagctgagc ctccttacct

1741 cccttcagcc aagccccacc tgcacgtgat ctgctggccc tcaggctgct gctctgcctt

1801 cattgctgga gacagtagag gcatgaacac acatggatgc acacacacac acgccaatgc

1861 acacacacag agatatgcac acacacggat gcacacacag atggtcacac agagatacgc

1921 aaacacaccg atgcacacgc acatagagat atgcacacac agatgcacac acagatatac

1981 acatggatgc acgcacatgc caatgcacgc acacatcagt gcacacggat gcacagagat

2041 atgcacacac cgatgtgcgc acacacagat atgcacacac atggatgagc acacacacac

2101 caagtgcgca cacacaccga tgtacacaca cagatgcaca cacagatgca cacacaccga

2161 tgctgactcc atgtgtgctg tcctctgaag gcggttgttt agctctcact tttctggttc

2221 ttatccatta tcatcttcac ttcagacaat tcagaagcat caccatgcat ggtggcgaat

2281 gcccccaaac tctcccccaa atgtatttct cccttcgctg ggtgccgggc tgcacagact

2341 attccccacc tgcttcccag cttcacaata aacggctgcg tctcctccgc acacctgtgg

2401 tgcctgccac cc

Homo sapiens coagulation factor V (proaccelerin, labile factor)

(F5), mRNA.

ACCESSION NM_000130

VERSION NM_000130.2 GI:10518500

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TFSPYEDEVNSSFTSGRNNTMIRAVQPGETYTYKWNILEFDEPTENDAQCLTRPYYSD

VDIMRDIASGLIGLLLICKSRSLDRRGIQRAADIEQQAVFAVFDENKSWYLEDNINKF

CENPDEVKRDDPKFYESNIMSTINGYVPESITTLGFCFDDTVQWHFCSVGTQNEILTI

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1 tcattgcagc tgggacagcc cggagtgtgg ttagcagctc ggcaagcgct gcccaggtcc

61 tggggtggtg gcagccagcg ggagcaggaa aggaagcatg ttcccaggct gcccacgcct

121 ctgggtcctg gtggtcttgg gcaccagctg ggtaggctgg gggagccaag ggacagaagc

181 ggcacagcta aggcagttct acgtggctgc tcagggcatc agttggagct accgacctga

241 gcccacaaac tcaagtttga atctttctgt aacttccttt aagaaaattg tctacagaga

301 gtatgaacca tattttaaga aagaaaaacc acaatctacc atttcaggac ttcttgggcc

361 tactttatat gctgaagtcg gagacatcat aaaagttcac tttaaaaata aggcagataa

421 gcccttgagc atccatcctc aaggaattag gtacagtaaa ttatcagaag gtgcttctta

481 ccttgaccac acattccctg cagagaagat ggacgacgct gtggctccag gccgagaata

541 cacctatgaa tggagtatca gtgaggacag tggacccacc catgatgacc ctccatgcct

601 cacacacatc tattactccc atgaaaatct gatcgaggat ttcaactctg ggctgattgg

661 gcccctgctt atctgtaaaa aagggaccct aactgagggt gggacacaga agacgtttga

721 caagcaaatc gtgctactat ttgctgtgtt tgatgaaagc aagagctgga gccagtcatc

781 atccctaatg tacacagtca atggatatgt gaatgggaca atgccagata taacagtttg

841 tgcccatgac cacatcagct ggcatctgct gggaatgagc tcggggccag aattattctc

901 cattcatttc aacggccagg tcctggagca gaaccatcat aaggtctcag ccatcaccct

961 tgtcagtgct acatccacta ccgcaaatat gactgtgggc ccagagggaa agtggatcat

1021 atcttctctc accccaaaac atttgcaagc tgggatgcag gcttacattg acattaaaaa

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1381 agacacactc aaaatcgtgt tcaaaaatat ggccagccgc ccctatagca tttaccctca

1441 tggagtgacc ttctcgcctt atgaagatga agtcaactct tctttcacct caggcaggaa

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1561 agagtttgat gaacccacag aaaatgatgc ccagtgctta acaagaccat actacagtga

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1861 tatcaatggc tatgtgcctg agagcataac tactcttgga ttctgctttg atgacactgt

1921 ccagtggcac ttctgtagtg tggggaccca gaatgaaatt ttgaccatcc acttcactgg

1981 gcactcattc atctatggaa agaggcatga ggacaccttg accctcttcc ccatgcgtgg

2041 agaatctgtg acggtcacaa tggataatgt tggaacttgg atgttaactt ccatgaattc

2101 tagtccaaga agcaaaaagc tgaggctgaa attcagggat gttaaatgta tcccagatga

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CELLTH-009

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2281 cagactggct gcagcattag gaattaggtc attccgaaac tcatcattga accaggaaga

2341 agaagagttc aatcttactg ccctagctct ggagaatggc actgaattcg tttcttcgaa

2401 cacagatata attgttggtt caaattattc ttccccaagt aatattagta agttcactgt

2461 caataacctt gcagaacctc agaaagcccc ttctcaccaa caagccacca cagctggttc

2521 cccactgaga cacctcattg gcaagaactc agttctcaat tcttccacag cagagcattc

2581 cagcccatat tctgaagacc ctatagagga tcctctacag ccagatgtca cagggatacg

2641 tctactttca cttggtgctg gagaattcag aagtcaagaa catgctaagc gtaagggacc

2701 caaggtagaa agagatcaag cagcaaagca caggttctcc tggatgaaat tactagcaca

2761 taaagttggg agacacctaa gccaagacac tggttctcct tccggaatga ggccctggga

2821 ggaccttcct agccaagaca ctggttctcc ttccagaatg aggccctggg aggaccctcc

2881 tagtgatctg ttactcttaa aacaaagtaa ctcatctaag attttggttg ggagatggca

2941 tttggcttct gagaaaggta gctatgaaat aatccaagat actgatgaag acacagctgt

3001 taacaattgg ctgatcagcc cccagaatgc ctcacgtgct tggggagaaa gcacccctct

3061 tgccaacaag cctggaaagc agagtggcca cccaaagttt cctagagtta gacataaatc

3121 tctacaagta agacaggatg gaggaaagag tagactgaag aaaagccagt ttctcattaa

3181 gacacgaaaa aagaaaaaag agaagcacac acaccatgct cctttatctc cgaggacctt

3241 tcaccctcta agaagtgaag cctacaacac attttcagaa agaagactta agcattcgtt

3301 ggtgcttcat aaatccaatg aaacatctct tcccacagac ctcaatcaga cattgccctc

3361 tatggatttt ggctggatag cctcacttcc tgaccataat cagaattcct caaatgacac

3421 tggtcaggca agctgtcctc caggtcttta tcagacagtg cccccagagg aacactatca

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3541 ctcttctcca gagctcagtg aaatgcttga gtatgaccga agtcacaagt ccttccccac

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4021 tcagacaaac ctttccccag ccctcggtca gatgcccatt tctccagacc tcagccatac

4081 aacccttttct ctagacttca gccagacaaa cctctctcca gaactcagtc aaacaaacct

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4201 agacctcagc cagacaaacc tctctccaga actcagtcag acaaaccttt ccccagacct

4261 cagtgagatg cccctctttg cagatctcag tcaaattccc cttaccccag acctcgacca

4321 gatgacactt tctccagacc ttggtgagac agatctttcc ccaaactttg gtcagatgtc

4381 cctttcccca gacctcagcc aggtgactct ctctccagac atcagtgaca ccacccttct

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4561 tcagatgcca tctccttcat ctcctactct caatgatact tttctatcaa aggaatttaa

4621 tccactggtt atagtgggcc tcagtaaaga tggtacagat tacattgaga tcattccaaa

4681 ggaagaggtc cagagcagtg aagatgacta tgctgaaatt gattatgtgc cctatgatga

4741 cccctacaaa actgatgtta ggacaaacat caactcctcc agagatcctg acaacattgc

4801 agcatggtac ctccgcagca acaatggaaa cagaagaaat tattacattg ctgctgaaga

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4921 tattccagaa gataccacat ataagaaagt agtttttcga aagtacctcg acagcacttt

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5221 cgtatggcat gccactgagc gatcagggcc agaaagtcct ggctctgcct gtcgggcttg

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6001 aaaggaagtc ataatcacag ggatccagac ccaaggtgcc aaacactacc tgaagtcctg

6061 ctataccaca gagttctatg tagcttacag ttccaaccag atcaactggc agatcttcaa

6121 agggaacagc acaaggaatg tgatgtattt taatggcaat tcagatgcct ctacaataaa

6181 agagaatcag tttgacccac ctattgtggc tagatatatt aggatctctc caactcgagc

6241 ctataacaga cctacccttc gattggaact gcaaggttgt gaggtaaatg gatgttccac

6301 acccctgggt atggaaaatg gaaagataga aaacaagcaa atcacagctt cttcgtttaa

6361 gaaatcttgg tggggagatt actgggaacc cttccgtgcc cgtctgaatg cccagggacg

6421 tgtgaatgcc tggcaagcca aggcaaacaa caataagcag tggctagaaa ttgatctact

6481 caagatcaag aagataacgg caattataac acagggctgc aagtctctgt cctctgaaat

6541 gtatgtaaag agctatacca tccactacag tgagcaggga gtggaatgga aaccatacag

6601 gctgaaatcc tccatggtgg acaagatttt tgaaggaaat actaatacca aaggacatgt

6661 gaagaacttt ttcaaccccc caatcatttc caggtttatc cgtgtcattc ctaaaacatg

6721 gaatcaaagt attgcacttc gcctggaact ctttggctgt gatatttact agaattgaac

6781 attcaaaaac ccctggaaga gactctttaa gacctcaaac catttagaat gggcaatgta

6841 ttttacgctg tgttaaatgt taacagtttt ccactatttc tctttctttt ctattagtga

6901 ataaaatttt atac

Homo sapiens coagulation factor II (thrombin) (F2), mRNA.

ACCESSION NM_000506

VERSION NM_000506.2 GI:5922005

MAHVRGLQLPGCLALAALCSLVHSQHVFLAPQQARSLLQRVRRA

NTFLEEVRKGNLERECVEETCSYEEAFEALESSTATDVFWAKYTACETARTPRDKLAA

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QQYQGRLAVTTHGLPCLAWASAQAKALSKHQDFNSAVQLVENFCRNPDGDEEGVWCYV

AGKPGDFGYCDLNYCEEAVEEETGDGLDEDSDRAIEGRTATSEYQTFFNPRTFGSGEA

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121 tcctcagcaa gcacggtcgc tgctccagcg ggtccggcga gccaacacct tcttggagga

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901 ttgtgaggag gccgtggagg aggagacagg agatgggctg gatgaggact cagacagggc

961 catcgaaggg cgtaccgcca ccagtgagta ccagactttc ttcaatccga ggacctttgg

1021 ctcgggagag gcagactgtg ggctgcgacc tctgttcgag aagaagtcgc tggaggacaa

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1321 ccgcacaagg tacgagcgaa acattgaaaa gatatccatg ttggaaaaga tctacatcca

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1621 tgtggagcgg ccggtctgca aggactccac ccggatccgc atcactgaca acatgttctg

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1801 gggtgaaggc tgtgaccggg atgggaaata tggcttctac acacatgtgt tccgcctgaa

1861 gaagtggata cagaaggtca ttgatcagtt tggagagtag gggccactca tattctgggc

1921 tcctggaacc aatcccgtga aagaattatt tttgtgtttc taaaactatg gttcccaata

1981 aaagtgactc tcagcgg

TABLE 6

```
Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu
 1               5                  10                  15

Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu His
            20                  25                  30

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

Tyr Ala Trp Lys Arg Met Glu Val Gly Gln Gln Ala Val Glu Val Trp
    50                  55                  60

Gln Gly Leu Ala Leu Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu
65                  70                  75                  80

Leu Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp
                85                  90                  95

Lys Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu
            100                 105                 110

Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala
        115                 120                 125

Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val
    130                 135                 140

Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala
145                 150                 155                 160

Cys Arg Thr Gly Asp
```

```
Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu
 1               5                  10                  15

Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu His
            20                  25                  30

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

Tyr Ala Trp Lys Arg Met Glu Val Gly Gln Gln Ala Val Glu Val Trp
    50                  55                  60

Gln Gly Leu Ala Leu Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu
65                  70                  75                  80

Leu Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp
                85                  90                  95

Lys Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu
            100                 105                 110
```

```
Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala
        115                 120                 125

Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val
    130                 135                 140

Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala
145                 150                 155                 160

Cys Arg Thr Gly Asp Arg
                165
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TABLE 7

AAY-AAY-ACN, ACN-AAY-AAY, AAY-ACN-AAY, AAY-AAY-AAY-ACN, ACN-AAY-AAY-AAY, AAY-ACN-AAY-AAY, AAY-AAY-ACN-AAY, AAY-AAY-AAY-AAY-ACN, ACN-AAY-AAY-AAY-AAY, AAY-ACN-AAY-AAY-AAY, AAY-AAY-ACN-AAY-AAY, AAY-AAY-AAY-ACN-AAY, AAY-AAY-AAY-ACN-ACN, ACN-ACN-AAY-AAY-AAY, ACN-AAY-ACN-AAY-AAY, ACN-AAY-AAY-ACN-AAY, ACN-AAY-AAY-AAY-ACN, AAY-ACN-ACN-AAY-AAY, AAY-ACN-AAY-ACN-AAY, AAY-ACN-AAY-AAY-ACN, AAY-AAY-ACN-ACN-AAY, AAY-AAY-ACN-AAY-ACN, ACN-AAY-AAY-AAY-AAY-AAY, AAY-ACN-AAY-AAY-AAY-AAY, AAY-AAY-ACN-AAY-AAY-AAY, AAY-AAY-ACN-AAY-AAY, AAY-AAY-AAY-AAY-ACN-AAY, AAY-AAY-AAY-AAY-ACN-ACN, ACN-ACN-AAY-AAY-AAY-AAY, ACN-AAY-ACN-AAY-AAY-AAY, ACN-AAY-AAY-ACN-AAY-AAY, ACN-AAY-AAY-AAY-ACN-AAY, ACN-AAY-AAY-AAY-ACN, ACN-AAY-ACN-ACN-AAY-AAY, AAY-ACN-AAY-ACN-AAY, AAY-ACN-AAY-AAY-AAY-ACN, AAY-AAY-ACN-ACN-AAY-AAY, AAY-AAY-ACN-AAY-ACN-AAY, AAY-AAY-ACN-AAY-ACN, AAY-AAY-AAY-ACN-ACN-AAY, AAY-AAY-AAY-ACN-AAY-ACN, AAY-AAY-AAY-AAY-ACN-ACN-ACN, ACN-ACN-ACN-AAY-AAY-AAY, ACN-AAY-ACN-ACN-AAY-AAY-AAY, ACN-AAY-ACN-AAY-ACN-AAY, ACN-AAY-ACN-AAY-AAY-ACN-AAY, ACN-AAY-ACN-AAY-AAY-AAY-ACN, ACN-AAY-AAY-ACN-ACN-AAY-AAY, ACN-AAY-AAY-ACN-AAY-AAY, ACN-AAY-AAY-AAY-ACN-AAY, ACN-AAY-AAY-AAY-ACN, ACN-AAY-AAY-AAY-ACN-ACN-AAY, ACN-AAY-AAY-AAY-AAY-ACN-ACN, ACN-ACN-AAY-ACN-AAY-AAY-AAY, ACN-ACN-AAY-AAY-ACN-AAY-AAY, ACN-ACN-AAY-AAY-AAY-ACN-AAY, ACN-ACN-AAY-AAY-AAY-AAY-ACN, AAY-ACN-ACN-ACN-AAY-AAY-AAY, AAY-ACN-ACN-AAY-ACN-AAY-AAY, AAY-ACN-ACN-AAY-AAY-ACN-AAY, AAY-ACN-ACN-AAY-AAY-AAY-ACN, AAY-ACN-AAY-ACN-ACN-AAY-AAY, AAY-ACN-AAY-AAY-ACN-ACN-AAY, AAY-ACN-AAY-ACN-AAY-AAY-ACN, AAY-ACN-AAY-ACN-AAY-ACN-ACN, AAY-ACN-AAY-AAY-AAY-ACN-ACN, AAY-ACN-AAY-ACN-AAY-AAY-ACN, AAY-ACN-AAY-AAY-ACN-AAY-ACN, AAY-AAY-ACN-ACN-ACN-AAY-AAY, AAY-AAY-ACN-ACN-AAY-ACN-AAY, AAY-AAY-ACN-AAY-ACN-ACN-AAY, AAY-AAY-ACN-AAY-ACN-AAY-ACN, AAY-AAY-ACN-AAY-ACN-AAY-ACN, AAY-AAY-ACN-AAY-AAY-

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AAY-ACN- AAY-AAY-AAY-AAY-AAY-AAY-ACN, ACN-AAY-AAY-AAY-AAY-
AAY-AAY, AAY-ACN-AAY-AAY-AAY-AAY-AAY, AAY-AAY-ACN-AAY-AAY-
AAY-AAY, AAY-AAY-AAY-ACN-AAY-AAY-AAY, AAY-AAY-AAY-AAY-ACN-
AAY-AAY, AAY-AAY-AAY-AAY-AAY-ACN-AAY

Oligonucleotides of peptide motifs containing 3-7 amino acid residues with N(Asparagine) as the major constituent and A(Alanine) as the minor constituent

AAY-AAY-GCN, GCN-AAY-AAY, AAY-GCN-AAY, AAY-AAY-AAY-GCN, GCN-
AAY-AAY-AAY, AAY-GCN-AAY-AAY, AAY-AAY-GCN-AAY, AAY-AAY-AAY-
AAY-GCN, GCN-AAY-AAY-AAY-AAY, AAY-GCN-AAY-AAY-AAY, AAY-AAY-
GCN-AAY-AAY, AAY-AAY-AAY-GCN-AAY, AAY-AAY-AAY-GCN-GCN, GCN-
GCN-AAY-AAY-AAY, GCN-AAY-GCN-AAY-AAY, GCN-AAY-AAY-GCN-AAY,
GCN-AAY-AAY-AAY-GCN, AAY-GCN-GCN-AAY-AAY, AAY-GCN-AAY-GCN-
AAY, AAY-GCN-AAY-AAY-GCN, AAY-AAY-GCN-GCN-AAY, AAY-AAY-GCN-
AAY-GCN, AAY-AAY-AAY-AAY-AAY-GCN, GCN-AAY-AAY-AAY-AAY-AAY,
AAY-GCN-AAY-AAY-AAY-AAY, AAY-AAY-GCN-AAY-AAY-AAY, AAY-AAY-
AAY-GCN-AAY-AAY, AAY-AAY-AAY-AAY-GCN-AAY, AAY-AAY-AAY-AAY-
GCN-GCN, GCN-GCN-AAY-AAY-AAY-AAY, GCN-AAY-GCN-AAY-AAY-AAY,
GCN-AAY-AAY-GCN-AAY-AAY, GCN-AAY-AAY-AAY-GCN-AAY, GCN-AAY-
AAY-AAY-AAY-GCN, AAY-GCN-GCN-AAY-AAY-AAY, AAY-GCN-AAY-GCN-

AAY-AAY, AAY-GCN-AAY-AAY-GCN-AAY, AAY-GCN-AAY-AAY-AAY-GCN, AAY-AAY-GCN-GCN-AAY-AAY, AAY-AAY-GCN-AAY-GCN-AAY, AAY-AAY-GCN-AAY-AAY-GCN, AAY-AAY-AAY-GCN-GCN-AAY, AAY-AAY-AAY-GCN-AAY-GCN, AAY-AAY-AAY-AAY-GCN-GCN-GCN, GCN-GCN-GCN-AAY-AAY-AAY-AAY, GCN-AAY-GCN-GCN-AAY-AAY-AAY, GCN-AAY-GCN-AAY-GCN-AAY-AAY, GCN-AAY-GCN-AAY-AAY-GCN-AAY, GCN-AAY-GCN-AAY-AAY-AAY-GCN, GCN-AAY-AAY-GCN-GCN-AAY-AAY, GCN-AAY-AAY-GCN-AAY-GCN-AAY, GCN-AAY-AAY-GCN-AAY-AAY-GCN, GCN-AAY-AAY-AAY-GCN-AAY-GCN, GCN-AAY-AAY-AAY-GCN-GCN-AAY, GCN-AAY-AAY-AAY-AAY-GCN-GCN, GCN-GCN-AAY-GCN-AAY-AAY-AAY, GCN-GCN-AAY-AAY-GCN-AAY-AAY, GCN-GCN-AAY-AAY-AAY-GCN-AAY, GCN-GCN-AAY-AAY-AAY-GCN, AAY-GCN-GCN-GCN-AAY-AAY-AAY, AAY-GCN-GCN-AAY-GCN-AAY-AAY, AAY-GCN-GCN-AAY-GCN-AAY-AAY, AAY-GCN-GCN-AAY-AAY-GCN-AAY, AAY-GCN-AAY-GCN-GCN-AAY-AAY, AAY-GCN-AAY-AAY-GCN-GCN-AAY, AAY-GCN-AAY-AAY-AAY-GCN-GCN, AAY-GCN-AAY-GCN-AAY-AAY-GCN, AAY-GCN-AAY-AAY-GCN-AAY-GCN, AAY-AAY-GCN-GCN-GCN-AAY-AAY, AAY-AAY-GCN-GCN-AAY-AAY-GCN, AAY-AAY-GCN-AAY-GCN-AAY-GCN, AAY-AAY-GCN-AAY-AAY-GCN-GCN, AAY-AAY-AAY-GCN-GCN-GCN-AAY, AAY-AAY-AAY-GCN-AAY-GCN-GCN, AAY-AAY-AAY-AAY-AAY-GCN-GCN, GCN-GCN-AAY-AAY-AAY-AAY-AAY, GCN-AAY-GCN-AAY-AAY-AAY-AAY, GCN-AAY-AAY-GCN-AAY-AAY-AAY, GCN-AAY-AAY-AAY-AAY-GCN-AAY, GCN-AAY-AAY-AAY-AAY-AAY-GCN, AAY-GCN-GCN-AAY-AAY-AAY-AAY, AAY-GCN-AAY-GCN-AAY-AAY-AAY, AAY-GCN-AAY-AAY-GCN-AAY-AAY, AAY-GCN-AAY-AAY-AAY-GCN-AAY, AAY-GCN-AAY-AAY-AAY-AAY-GCN, AAY-AAY-GCN-AAY-GCN-AAY-AAY, AAY-AAY-GCN-AAY-AAY-GCN-AAY, AAY-AAY-GCN-AAY-AAY-AAY-GCN, AAY-AAY-AAY-GCN-AAY-GCN-AAY, AAY-AAY-AAY-GCN-AAY-AAY-GCN, AAY-AAY-AAY-AAY-GCN-AAY-GCN, AAY-AAY-AAY-AAY-AAY-AAY-GCN, GCN-AAY-AAY-AAY-AAY-AAY, AAY-GCN-AAY-AAY-AAY-AAY-AAY, AAY-AAY-GCN-AAY-AAY-AAY, AAY-AAY-AAY-GCN-AAY-GCN-AAY, AAY-AAY-AAY-AAY-GCN-GCN-AAY, AAY-AAY-AAY-AAY-AAY-AAY-GCN, GCN-AAY-AAY-AAY-AAY-AAY, AAY-AAY-GCN-AAY-AAY-AAY-AAY

AAY-AAY, AAY-AAY-AAY-GCN-AAY-AAY-AAY, AAY-AAY-AAY-AAY-GCN-AAY-AAY, AAY-AAY-AAY-AAY-AAY-GCN-AAY

AAY-AAY-AGY, AGY-AAY-AAY, AAY-AGY-AAY, AAY-AAY-AAY-AGY, AGY-AAY-AAY-AAY, AAY-AGY-AAY-AAY, AAY-AAY-AGY-AAY, AAY-AAY-AAY-AAY-AGY, AGY-AAY-AAY-AAY-AAY, AAY-AGY-AAY-AAY-AAY, AAY-AAY-AGY-AAY-AAY, AAY-AAY-AAY-AGY-AAY, AAY-AAY-AAY-AGY-AGY, AGY-AGY-AAY-AAY-AAY, AGY-AAY-AGY-AAY-AAY, AGY-AAY-AAY-AGY-AAY, AGY-AAY-AAY-AAY-AGY, AAY-AGY-AGY-AAY-AAY, AAY-AGY-AAY-AGY-AAY, AAY-AGY-AAY-AAY-AGY, AAY-AAY-AGY-AGY-AAY, AAY-AAY-AGY-AAY-AGY, AGY-AAY-AAY-AAY-AAY-AAY, AAY-AGY-AAY-AAY-AAY-AAY, AAY-AAY-AGY-AAY-AAY-AAY, AAY-AAY-AAY-AGY-AAY-AAY, AAY-AAY-AAY-AAY-AGY-AAY, AAY-AAY-AAY-AAY-AGY-AGY, AGY-AGY-AAY-AAY-AAY-AAY, AGY-AAY-AGY-AAY-AAY-AAY, AGY-AAY-AAY-AGY-AAY-AAY, AGY-AAY-AAY-AAY-AGY-AAY, AGY-AAY-AAY-AGY-AAY-AAY, AAY-AGY-AGY-AAY-AAY-AAY, AAY-AGY-AAY-AGY-AAY-AAY, AAY-AGY-AAY-AAY-AGY-AAY, AAY-AAY-AGY-AGY-AAY-AAY, AAY-AAY-AGY-AAY-AGY-AAY, AAY-AAY-AGY-AGY-AAY-AAY, AAY-AAY-AAY-AGY-AGY-AAY, AAY-AAY-AAY-AGY-AGY-AAY, AAY-AAY-AAY-AGY-AGY, AGY-AGY-AGY-AAY-AAY-AAY, AGY-AAY-AGY-AGY-AAY-AAY-AAY, AGY-AAY-AGY-AAY-AGY-AAY, AGY-AAY-AGY-AAY-AAY-AGY-AAY, AGY-AAY-AGY-AAY-AAY-AAY, AGY-AAY-AAY-AGY-AGY-AAY-AAY, AGY-AAY-AAY-AGY-AGY-AAY, AGY-AAY-AAY-AGY-AAY-AAY-AGY, AGY-AAY-AAY-AAY-AGY-AAY, AGY-AAY-AAY-AAY-AGY-AGY-AAY, AGY-AAY-AAY-AAY-AAY-AGY, AGY-AGY-AAY-AGY-AAY-AAY-AAY, AGY-AGY-AAY-AAY-AGY-AAY, AGY-AGY-AAY-AAY-AAY-AGY-AAY, AGY-AGY-AAY-AAY-AAY-AAY, AAY-AGY-AGY-AGY-AAY-AAY-AAY, AAY-AGY-AGY-AAY-AGY-AAY, AAY-AGY-AGY-AAY-AAY-AGY-AAY, AAY-AGY-AGY-AAY-AAY-AAY, AAY-AGY-AAY-AGY-AGY-AAY-AAY, AAY-AGY-AAY-AAY-AGY-AGY, AAY-AGY-AAY-AAY-AAY-AGY-AGY, AAY-AGY-AAY-AGY-AAY-AAY-AGY, AAY-AGY-AAY-AGY-AAY-AAY, AAY-AAY-AGY-AGY-AGY-AAY-AAY, AAY-AAY-AGY-AGY-AAY-AGY, AAY-AAY-AGY-AGY-AAY-AAY-AGY, AAY-AAY-AGY-AAY-AGY-

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Oligonucleotides of peptide motifs containing 3-7 amino acid residues with N(Asparagine) as the major constituent and Q(Glutamine) as the minor constituent

AAY-AAY-CAR, CAR-AAY-AAY, AAY-CAR-AAY, AAY-AAY-AAY-CAR, CAR-AAY-AAY-AAY, AAY-CAR-AAY-AAY, AAY-AAY-CAR-AAY, AAY-AAY-AAY-AAY-CAR, CAR-AAY-AAY-AAY-AAY, AAY-CAR-AAY-AAY-AAY, AAY-AAY-CAR-AAY-AAY, AAY-AAY-AAY-CAR-AAY, AAY-AAY-AAY-CAR-CAR, CAR-CAR-AAY-AAY-AAY, CAR-AAY-CAR-AAY-AAY, CAR-AAY-AAY-CAR-AAY, CAR-AAY-AAY-AAY-CAR, AAY-CAR-CAR-AAY-AAY, AAY-CAR-AAY-CAR-AAY, AAY-CAR-AAY-AAY-CAR, AAY-AAY-CAR-CAR-AAY, AAY-AAY-CAR-AAY-CAR, AAY-AAY-AAY-AAY-AAY-CAR, CAR-AAY-AAY-AAY-AAY-AAY, AAY-CAR-AAY-AAY-AAY-AAY, AAY-AAY-CAR-AAY-AAY-AAY, AAY-AAY-AAY-CAR-AAY-AAY, AAY-AAY-AAY-AAY-CAR-AAY, CAR-CAR-AAY-AAY-AAY-AAY, CAR-AAY-CAR-AAY-AAY-AAY, CAR-AAY-AAY-CAR-AAY-AAY, CAR-AAY-AAY-AAY-CAR-AAY, CAR-AAY-

AAY-AAY-AAY-CAR, AAY-CAR-CAR-AAY-AAY-AAY, AAY-CAR-AAY-CAR-AAY-AAY, AAY-CAR-AAY-AAY-CAR-AAY, AAY-CAR-AAY-AAY-AAY-CAR, AAY-AAY-CAR-CAR-AAY-AAY, AAY-AAY-CAR-AAY-CAR-AAY, AAY-AAY-CAR-AAY-AAY-CAR, AAY-AAY-AAY-CAR-CAR-AAY, AAY-AAY-AAY-CAR-AAY-CAR, AAY-AAY-AAY-AAY-CAR-CAR-CAR, CAR-CAR-CAR-AAY-AAY-AAY-AAY, CAR-AAY-CAR-CAR-AAY-AAY-AAY, CAR-AAY-CAR-AAY-CAR-AAY-AAY, CAR-AAY-CAR-AAY-AAY-CAR-AAY, CAR-AAY-CAR-AAY-AAY-AAY-CAR, CAR-AAY-AAY-CAR-CAR-AAY-AAY, CAR-AAY-AAY-CAR-AAY-CAR-AAY, CAR-AAY-AAY-CAR-AAY-AAY-CAR, CAR-AAY-AAY-CAR-AAY-AAY-CAR-AAY, CAR-AAY-AAY-AAY-CAR-CAR-AAY, CAR-AAY-AAY-AAY-AAY-CAR-CAR, CAR-CAR-AAY-CAR-AAY-AAY-AAY, CAR-CAR-AAY-AAY-CAR-AAY-AAY, CAR-CAR-AAY-AAY-AAY-CAR-AAY, CAR-CAR-AAY-AAY-AAY-AAY-CAR, AAY-CAR-CAR-CAR-AAY-AAY-AAY, AAY-CAR-CAR-AAY-CAR-AAY-AAY, AAY-CAR-CAR-AAY-AAY-CAR-AAY, AAY-CAR-CAR-AAY-AAY-AAY-CAR, AAY-CAR-AAY-CAR-CAR-AAY-AAY, AAY-CAR-AAY-AAY-CAR-CAR-AAY, AAY-CAR-AAY-AAY-AAY-CAR-CAR, AAY-CAR-AAY-CAR-AAY-CAR-AAY, AAY-CAR-AAY-CAR-AAY-AAY-CAR, AAY-CAR-AAY-AAY-CAR-AAY-CAR, AAY-AAY-CAR-CAR-CAR-AAY-AAY, AAY-AAY-CAR-CAR-AAY-CAR-AAY, AAY-AAY-CAR-CAR-AAY-AAY-CAR, AAY-AAY-CAR-AAY-CAR-AAY-CAR, AAY-AAY-CAR-AAY-CAR-AAY-AAY-CAR, AAY-AAY-AAY-CAR-CAR-CAR-AAY, AAY-AAY-AAY-CAR-CAR-AAY-CAR, AAY-AAY-AAY-CAR-AAY-CAR-CAR, AAY-AAY-AAY-AAY-AAY-CAR-CAR, CAR-CAR-AAY-AAY-AAY-AAY-AAY, CAR-AAY-CAR-AAY-AAY-AAY-AAY, CAR-AAY-AAY-CAR-AAY-AAY-AAY, CAR-AAY-AAY-AAY-CAR-AAY-AAY, CAR-AAY-AAY-AAY-AAY-CAR-AAY, CAR-AAY-AAY-AAY-AAY-AAY-CAR, AAY-CAR-CAR-AAY-AAY-AAY-AAY, AAY-CAR-AAY-CAR-AAY-AAY-AAY, AAY-CAR-AAY-AAY-CAR-AAY-AAY, AAY-CAR-AAY-AAY-AAY-AAY-CAR, AAY-AAY-CAR-CAR-AAY-AAY-AAY, AAY-AAY-CAR-AAY-CAR-AAY-AAY, AAY-AAY-CAR-AAY-AAY-CAR-AAY, AAY-AAY-CAR-AAY-AAY-AAY-CAR, AAY-AAY-AAY-CAR-CAR-AAY-AAY, AAY-AAY-AAY-CAR-AAY-CAR-AAY, AAY-AAY-AAY-AAY-CAR-CAR-AAY, AAY-AAY-AAY-AAY-AAY-CAR-CAR, CAR-AAY-AAY-AAY-AAY-AAY-CAR,

AAY-AAY, AAY-CAR-AAY-AAY-AAY-AAY-AAY, AAY-AAY-CAR-AAY-AAY-AAY-AAY, AAY-AAY-AAY-CAR-AAY-AAY-AAY, AAY-AAY-AAY-AAY-CAR-AAY-AAY, AAY-AAY-AAY-AAY-AAY-CAR-AAY

Oligonucleotides of peptide motifs containing 3-7 amino acid residues with N(Asparagine) as the major constituent and E(Glutamic Acid) as the minor constituent

AAY-AAY-GAR, GAR-AAY-AAY, AAY-GAR-AAY, AAY-AAY-AAY-GAR, GAR-AAY-AAY-AAY, AAY-GAR-AAY-AAY, AAY-AAY-GAR-AAY, AAY-AAY-AAY-AAY-GAR, GAR-AAY-AAY-AAY-AAY, AAY-GAR-AAY-AAY-AAY, AAY-AAY-GAR-AAY-AAY, AAY-AAY-AAY-GAR-AAY, AAY-AAY-AAY-GAR-GAR, GAR-GAR-AAY-AAY-AAY, GAR-AAY-GAR-AAY-AAY, GAR-AAY-AAY-GAR-AAY, GAR-AAY-AAY-AAY-GAR, AAY-GAR-GAR-AAY-AAY, AAY-GAR-AAY-GAR-AAY, AAY-GAR-AAY-AAY-GAR, AAY-AAY-GAR-GAR-AAY, AAY-AAY-GAR-AAY-GAR, AAY-AAY-AAY-AAY-AAY-GAR, GAR-AAY-AAY-AAY-AAY-AAY, AAY-GAR-AAY-AAY-AAY-AAY, AAY-AAY-GAR-AAY-AAY-AAY, AAY-AAY-AAY-GAR-AAY-AAY, AAY-AAY-AAY-GAR-AAY, AAY-AAY-AAY-AAY-GAR-GAR, GAR-GAR-AAY-AAY-AAY-AAY, GAR-AAY-GAR-AAY-AAY-AAY, GAR-AAY-AAY-GAR-AAY-AAY, GAR-AAY-AAY-AAY-GAR-AAY, GAR-AAY-AAY-AAY-AAY-GAR, AAY-GAR-GAR-AAY-AAY-AAY, AAY-GAR-AAY-GAR-AAY-AAY, AAY-GAR-AAY-AAY-GAR-AAY, AAY-GAR-AAY-AAY-AAY-GAR, AAY-AAY-GAR-GAR-AAY-AAY, AAY-AAY-GAR-AAY-GAR-AAY, AAY-AAY-GAR-AAY-AAY-GAR, AAY-AAY-AAY-GAR-GAR-AAY, AAY-AAY-AAY-GAR-AAY-GAR, AAY-AAY-AAY-AAY-GAR-GAR-GAR, GAR-GAR-GAR-AAY-AAY-AAY-AAY, GAR-AAY-GAR-GAR-AAY-AAY-AAY, GAR-AAY-GAR-AAY-GAR-AAY-AAY, GAR-AAY-GAR-AAY-AAY-GAR-AAY, GAR-AAY-GAR-AAY-AAY-AAY-GAR, GAR-AAY-AAY-GAR-GAR-AAY-AAY, GAR-AAY-AAY-GAR-AAY-GAR-AAY, GAR-AAY-AAY-GAR-AAY-AAY-GAR, GAR-AAY-AAY-AAY-GAR-GAR-AAY, GAR-AAY-AAY-AAY-AAY-GAR-GAR, GAR-GAR-AAY-GAR-AAY-AAY-AAY, GAR-GAR-AAY-AAY-GAR-AAY-AAY, GAR-GAR-AAY-AAY-AAY-GAR-AAY, GAR-GAR-AAY-AAY-AAY-AAY-GAR, AAY-GAR-GAR-GAR-AAY-AAY-AAY, AAY-GAR-GAR-AAY-GAR-AAY-AAY, AAY-GAR-GAR-AAY-AAY-GAR-AAY, AAY-GAR-GAR-AAY-AAY-

AAY-GAR, AAY-GAR-AAY-GAR-GAR-AAY-AAY, AAY-GAR-AAY-AAY-GAR-GAR-AAY, AAY-GAR-AAY-AAY-AAY-GAR-GAR, AAY-GAR-AAY-GAR-AAY-GAR-AAY, AAY-GAR-AAY-GAR-AAY-AAY-GAR, AAY-GAR-AAY-AAY-GAR-AAY-GAR, AAY-AAY-GAR-GAR-GAR-AAY-AAY, AAY-AAY-GAR-GAR-AAY-GAR-AAY, AAY-AAY-GAR-GAR-AAY-AAY-GAR, AAY-AAY-GAR-AAY-GAR-GAR-AAY, AAY-AAY-GAR-AAY-GAR-AAY-GAR, AAY-AAY-GAR-AAY-AAY-GAR-GAR, AAY-AAY-AAY-GAR-GAR-GAR-AAY, AAY-AAY-AAY-GAR-GAR-AAY-AAY, AAY-AAY-AAY-GAR-AAY-GAR-GAR, AAY-AAY-AAY-AAY-AAY-GAR-GAR, GAR-GAR-AAY-AAY-AAY-AAY-AAY, GAR-AAY-GAR-AAY-AAY-AAY-AAY, GAR-AAY-AAY-GAR-AAY-AAY-AAY, GAR-AAY-AAY-AAY-GAR-AAY-AAY, GAR-AAY-AAY-AAY-AAY-GAR-AAY, GAR-AAY-AAY-AAY-AAY-AAY-GAR, AAY-GAR-GAR-AAY-AAY-AAY-AAY, AAY-GAR-AAY-GAR-AAY-AAY-AAY, AAY-GAR-AAY-AAY-GAR-AAY-AAY, AAY-GAR-AAY-AAY-AAY-AAY-GAR, AAY-AAY-GAR-GAR-AAY-AAY-AAY, AAY-AAY-GAR-AAY-GAR-AAY-AAY, AAY-AAY-GAR-AAY-AAY-AAY-GAR, AAY-AAY-AAY-GAR-GAR-AAY-AAY, AAY-AAY-AAY-GAR-AAY-GAR-AAY, AAY-AAY-AAY-GAR-AAY-AAY, AAY-AAY-AAY-AAY-GAR-GAR-AAY, GAR-AAY-AAY-AAY-AAY-AAY-AAY, AAY-AAY-GAR-AAY-AAY-AAY-AAY-AAY, AAY-AAY-AAY-GAR-AAY-AAY-AAY, AAY-AAY-AAY-AAY-GAR-AAY-AAY, AAY-AAY-AAY-AAY-AAY-GAR-AAY

Oligonucleotides of peptide motifs containing 3-7 amino acid residues with N(Asparagine) as the major constituent and H(Histidine) as the minor constituent

AAY-AAY-CAY, CAY-AAY-AAY, AAY-CAY-AAY, AAY-AAY-AAY-CAY, CAY-AAY-AAY-AAY, AAY-CAY-AAY-AAY, AAY-AAY-CAY-AAY, AAY-AAY-AAY-AAY-CAY, CAY-AAY-AAY-AAY-AAY, AAY-CAY-AAY-AAY-AAY, AAY-AAY-CAY-AAY-AAY, AAY-AAY-AAY-CAY-AAY, AAY-AAY-AAY-CAY-CAY, CAY-CAY-AAY-AAY-AAY, CAY-AAY-CAY-AAY-AAY, CAY-AAY-AAY-CAY-AAY, CAY-AAY-AAY-AAY-CAY, AAY-CAY-CAY-AAY-AAY, AAY-CAY-AAY-CAY-AAY, AAY-CAY-AAY-AAY-CAY, AAY-AAY-CAY-CAY-AAY, AAY-AAY-CAY-

AAY-CAY, AAY-AAY-AAY-AAY-AAY-CAY, CAY-AAY-AAY-AAY-AAY-AAY,
AAY-CAY-AAY-AAY-AAY-AAY, AAY-AAY-CAY-AAY-AAY-AAY, AAY-AAY-
AAY-CAY-AAY-AAY, AAY-AAY-AAY-AAY-CAY-AAY, AAY-AAY-AAY-AAY-
CAY-CAY, CAY-CAY-AAY-AAY-AAY-AAY, CAY-AAY-CAY-AAY-AAY-AAY,
CAY-AAY-AAY-CAY-AAY-AAY, CAY-AAY-AAY-AAY-CAY-AAY, CAY-AAY-
AAY-AAY-AAY-CAY, AAY-CAY-CAY-AAY-AAY-AAY, AAY-CAY-AAY-CAY-
AAY-AAY, AAY-CAY-AAY-AAY-CAY-AAY, AAY-CAY-AAY-AAY-AAY-CAY,
AAY-AAY-CAY-CAY-AAY-AAY, AAY-AAY-CAY-AAY-CAY-AAY, AAY-AAY-
CAY-AAY-AAY-CAY, AAY-AAY-AAY-CAY-CAY-AAY, AAY-AAY-AAY-CAY-
AAY-CAY, AAY-AAY-AAY-AAY-CAY-CAY-CAY, CAY-CAY-CAY-AAY-AAY-
AAY-AAY, CAY-AAY-CAY-CAY-AAY-AAY-AAY, CAY-AAY-CAY-AAY-CAY-
AAY-AAY, CAY-AAY-CAY-AAY-AAY-CAY-AAY, CAY-AAY-CAY-AAY-AAY-
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CAY-AAY, CAY-AAY-AAY-CAY-AAY-AAY-CAY, CAY-AAY-AAY-AAY-CAY-
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CAY-CAY, CAY-CAY-AAY-CAY-AAY-AAY-AAY, CAY-CAY-AAY-AAY-CAY-
AAY-AAY, CAY-CAY-AAY-AAY-AAY-CAY-AAY, CAY-CAY-AAY-AAY-AAY-
AAY-CAY, AAY-CAY-CAY-CAY-AAY-AAY-AAY, AAY-CAY-CAY-AAY-CAY-
AAY-AAY, AAY-CAY-CAY-AAY-AAY-CAY-AAY, AAY-CAY-CAY-AAY-AAY-
AAY-CAY, AAY-CAY-AAY-CAY-CAY-AAY-AAY, AAY-CAY-AAY-AAY-CAY-
CAY-AAY, AAY-CAY-AAY-AAY-AAY-CAY-CAY, AAY-CAY-AAY-CAY-AAY-
CAY-AAY, AAY-CAY-AAY-CAY-AAY-AAY-CAY, AAY-CAY-AAY-AAY-CAY-
AAY-CAY, AAY-AAY-CAY-CAY-CAY-AAY-AAY, AAY-AAY-CAY-CAY-AAY-
CAY-AAY, AAY-AAY-CAY-CAY-AAY-AAY-CAY, AAY-AAY-CAY-AAY-CAY-
CAY-AAY, AAY-AAY-CAY-AAY-CAY-AAY-CAY, AAY-AAY-CAY-AAY-AAY-
CAY-CAY, AAY-AAY-AAY-CAY-CAY-CAY-AAY, AAY-AAY-AAY-CAY-CAY-
AAY-CAY, AAY-AAY-AAY-CAY-AAY-CAY-CAY, AAY-AAY-AAY-AAY-AAY-
CAY-CAY, CAY-CAY-AAY-AAY-AAY-AAY-AAY, CAY-AAY-CAY-AAY-AAY-
AAY-AAY, CAY-AAY-AAY-CAY-AAY-AAY-AAY, CAY-AAY-AAY-AAY-CAY-
AAY-AAY, CAY-AAY-AAY-AAY-AAY-CAY-AAY, CAY-AAY-AAY-AAY-AAY-
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AAY-AAY, AAY-CAY-AAY-AAY-CAY-AAY-AAY, AAY-CAY-AAY-AAY-AAY-
CAY-AAY, AAY-CAY-AAY-AAY-AAY-AAY-CAY, AAY-AAY-CAY-CAY-AAY-

AAY-AAY, AAY-AAY-CAY-AAY-CAY-AAY-AAY, AAY-AAY-CAY-AAY-AAY-CAY-AAY, AAY-AAY-CAY-AAY-AAY-AAY-CAY, AAY-AAY-AAY-CAY-CAY-AAY-AAY, AAY-AAY-AAY-CAY-AAY-CAY-AAY, AAY-AAY-AAY-CAY-AAY-AAY-CAY, AAY-AAY-AAY-AAY-CAY-CAY-AAY, AAY-AAY-AAY-AAY-CAY-AAY-CAY- AAY-AAY-AAY-AAY-AAY-AAY-CAY, CAY-AAY-AAY-AAY-AAY-AAY-AAY, AAY-CAY-AAY-AAY-AAY-AAY-AAY, AAY-AAY-CAY-AAY-AAY-AAY-AAY, AAY-AAY-AAY-CAY-AAY-AAY-AAY, AAY-AAY-AAY-AAY-CAY-AAY-AAY, AAY-AAY-AAY-AAY-AAY-CAY-AAY

AAY-AAY-GAY, GAY-AAY-AAY, AAY-GAY-AAY, AAY-AAY-AAY-GAY, GAY-AAY-AAY-AAY, AAY-GAY-AAY-AAY, AAY-AAY-GAY-AAY, AAY-AAY-AAY-AAY-GAY, GAY-AAY-AAY-AAY-AAY, AAY-GAY-AAY-AAY-AAY, AAY-AAY-GAY-AAY-AAY, AAY-AAY-AAY-GAY-AAY, AAY-AAY-AAY-GAY-GAY, GAY-GAY-AAY-AAY-AAY, GAY-AAY-GAY-AAY-AAY, GAY-AAY-AAY-GAY-AAY, GAY-AAY-AAY-AAY-GAY, AAY-GAY-GAY-AAY-AAY, AAY-GAY-AAY-GAY-AAY, AAY-GAY-AAY-AAY-GAY, AAY-AAY-GAY-GAY-AAY, AAY-AAY-GAY-AAY-GAY, AAY-AAY-AAY-AAY-AAY-GAY, GAY-AAY-AAY-AAY-AAY-AAY, AAY-GAY-AAY-AAY-AAY-AAY, AAY-AAY-GAY-AAY-AAY-AAY, AAY-AAY-AAY-GAY-AAY-AAY, AAY-AAY-AAY-AAY-GAY-AAY, GAY-GAY-AAY-AAY-AAY, GAY-AAY-GAY-AAY-AAY-AAY, GAY-AAY-AAY-GAY-AAY-AAY, GAY-AAY-AAY-AAY-GAY-AAY, GAY-AAY-AAY-AAY-AAY-GAY, GAY-GAY-GAY-AAY-AAY-AAY, GAY-AAY-GAY-GAY-AAY-AAY-AAY, GAY-AAY-GAY-AAY-GAY-AAY, GAY-AAY-GAY-AAY-AAY-GAY-AAY, GAY-AAY-AAY-GAY-GAY-AAY-AAY, GAY-AAY-AAY-GAY-AAY-AAY-GAY, GAY-AAY-AAY-AAY-GAY-GAY-AAY, GAY-AAY-AAY-AAY-AAY-GAY-GAY, GAY-GAY-AAY-GAY-AAY-AAY-AAY, GAY-GAY-AAY-AAY-GAY-AAY-AAY, GAY-GAY-AAY-AAY-AAY-GAY-AAY, GAY-GAY-AAY-AAY-AAY-AAY-GAY, AAY-GAY-GAY-GAY-AAY-AAY-AAY, AAY-GAY-GAY-AAY-GAY-

AAY-AAY, AAY-GAY-GAY-AAY-AAY-GAY-AAY, AAY-GAY-GAY-AAY-AAY-
AAY-GAY, AAY-GAY-AAY-GAY-GAY-AAY-AAY, AAY-GAY-AAY-AAY-GAY-
GAY-AAY, AAY-GAY-AAY-AAY-AAY-GAY-GAY, AAY-GAY-AAY-GAY-AAY-
GAY-AAY, AAY-GAY-AAY-GAY-AAY-AAY-GAY, AAY-GAY-AAY-AAY-GAY-
AAY-GAY, AAY-AAY-GAY-GAY-GAY-AAY-AAY, AAY-AAY-GAY-GAY-AAY-
GAY-AAY, AAY-AAY-GAY-GAY-AAY-AAY-GAY, AAY-AAY-GAY-AAY-GAY-
GAY-AAY, AAY-AAY-GAY-AAY-GAY-AAY-GAY, AAY-AAY-GAY-AAY-AAY-
GAY-GAY, AAY-AAY-AAY-GAY-GAY-GAY-AAY, AAY-AAY-AAY-GAY-GAY-
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GAY-GAY, GAY-GAY-AAY-AAY-AAY-AAY-AAY, GAY-AAY-GAY-AAY-AAY-
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AAY-GAY, AAY-GAY-GAY-AAY-AAY-AAY-AAY, AAY-GAY-AAY-GAY-AAY-
AAY-AAY, AAY-GAY-AAY-AAY-GAY-AAY-AAY, AAY-GAY-AAY-AAY-AAY-
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AAY-GAY- AAY-AAY-AAY-AAY-AAY-AAY-GAY, GAY-AAY-AAY-AAY-AAY-
AAY-AAY, AAY-GAY-AAY-AAY-AAY-AAY-AAY, AAY-AAY-GAY-AAY-AAY-
AAY-AAY, AAY-AAY-AAY-GAY-AAY-AAY-AAY, AAY-AAY-AAY-AAY-GAY-
AAY-AAY, AAY-AAY-AAY-AAY-AAY-GAY-AAY

G (glycine) as major constituent

GGN-GGN-ACN, ACN-GGN-GGN, GGN-ACN-GGN, GGN-GGN-GGN-ACN, ACN-
GGN-GGN-GGN, GGN-ACN-GGN-GGN, GGN-GGN-ACN-GGN, GGN-GGN-GGN-
GGN-ACN, ACN-GGN-GGN-GGN-GGN, GGN-ACN-GGN-GGN-GGN, GGN-GGN-
ACN-GGN-GGN, GGN-GGN-GGN-ACN-GGN, GGN-GGN-GGN-ACN-ACN, ACN-
ACN-GGN-GGN-GGN, ACN-GGN-ACN-GGN-GGN, ACN-GGN-GGN-ACN-GGN,
ACN-GGN-GGN-GGN-ACN, GGN-ACN-ACN-GGN-GGN, GGN-ACN-GGN-ACN-
GGN, GGN-ACN-GGN-GGN-ACN, GGN-GGN-ACN-ACN-GGN, GGN-GGN-ACN-
GGN-ACN, GGN-GGN-GGN-GGN-GGN-ACN, ACN-GGN-GGN-GGN-GGN-GGN,

GGN-ACN-GGN-GGN-GGN-GGN, GGN-GGN-ACN-GGN-GGN-GGN, GGN-GGN-GGN-ACN-GGN-GGN, GGN-GGN-GGN-GGN-ACN-GGN, GGN-GGN-GGN-GGN-ACN-ACN, ACN-ACN-GGN-GGN-GGN-GGN, ACN-GGN-ACN-GGN-GGN-GGN, ACN-GGN-GGN-ACN-GGN-GGN, ACN-GGN-GGN-GGN-ACN-GGN, ACN-GGN-GGN-GGN-GGN-ACN, GGN-ACN-ACN-GGN-GGN-GGN, GGN-ACN-GGN-ACN-GGN-GGN, GGN-ACN-GGN-GGN-ACN-GGN, GGN-ACN-GGN-GGN-GGN-ACN, GGN-GGN-ACN-ACN-GGN-GGN, GGN-GGN-ACN-GGN-ACN-GGN, GGN-GGN-ACN-GGN-GGN-ACN, GGN-GGN-GGN-ACN-ACN-GGN, GGN-GGN-GGN-ACN-GGN-ACN, GGN-GGN-GGN-GGN-ACN-ACN-ACN, ACN-ACN-ACN-GGN-GGN-GGN-GGN, ACN-GGN-ACN-ACN-GGN-GGN-GGN, ACN-GGN-ACN-GGN-ACN-GGN-GGN, ACN-GGN-ACN-GGN-GGN-ACN-GGN, ACN-GGN-ACN-GGN-GGN-GGN-ACN, ACN-GGN-GGN-ACN-ACN-GGN-GGN, ACN-GGN-GGN-ACN-GGN-ACN-GGN, ACN-GGN-GGN-ACN-GGN-GGN-ACN, ACN-GGN-GGN-GGN-ACN-GGN-ACN, ACN-GGN-GGN-GGN-ACN-ACN-GGN, ACN-GGN-GGN-GGN-GGN-ACN-ACN, ACN-ACN-GGN-ACN-GGN-GGN-GGN, ACN-ACN-GGN-GGN-ACN-GGN-GGN, ACN-ACN-GGN-GGN-GGN-ACN-GGN, ACN-ACN-GGN-GGN-GGN-GGN-ACN, GGN-ACN-ACN-ACN-GGN-GGN-GGN, GGN-ACN-ACN-GGN-ACN-GGN-GGN, GGN-ACN-ACN-GGN-GGN-ACN-GGN, GGN-ACN-ACN-GGN-GGN-GGN-ACN, GGN-ACN-GGN-ACN-ACN-GGN-GGN, GGN-ACN-GGN-GGN-ACN-ACN-GGN, GGN-ACN-GGN-GGN-GGN-ACN-ACN, GGN-ACN-GGN-ACN-GGN-ACN-GGN, GGN-ACN-GGN-ACN-GGN-GGN-ACN, GGN-ACN-GGN-GGN-ACN-GGN-ACN, GGN-GGN-ACN-ACN-ACN-GGN-GGN, GGN-GGN-ACN-ACN-GGN-ACN-GGN, GGN-GGN-ACN-ACN-GGN-GGN-ACN, GGN-GGN-ACN-GGN-ACN-ACN-GGN, GGN-GGN-ACN-GGN-ACN-GGN-ACN, GGN-GGN-ACN-GGN-GGN-ACN-ACN, GGN-GGN-GGN-ACN-ACN-ACN-GGN, GGN-GGN-GGN-ACN-ACN-GGN-ACN, GGN-GGN-GGN-ACN-GGN-ACN-ACN, GGN-GGN-GGN-GGN-GGN-ACN-ACN, ACN-ACN-GGN-GGN-GGN-GGN-GGN, ACN-GGN-ACN-GGN-GGN-GGN-GGN, ACN-GGN-GGN-ACN-GGN-GGN-GGN, ACN-GGN-GGN-GGN-ACN-GGN-GGN, ACN-GGN-GGN-GGN-GGN-ACN-GGN, ACN-GGN-GGN-GGN-GGN-GGN-ACN, GGN-ACN-ACN-GGN-GGN-GGN-GGN, GGN-ACN-GGN-ACN-GGN-GGN-GGN, GGN-ACN-GGN-GGN-ACN-GGN-GGN, GGN-ACN-GGN-GGN-GGN-ACN-GGN, GGN-ACN-GGN-GGN-GGN-GGN-ACN, GGN-GGN-ACN-ACN-GGN-GGN-GGN, GGN-GGN-ACN-GGN-ACN-GGN-GGN, GGN-GGN-ACN-GGN-GGN-

ACN-GGN, GGN-GGN-ACN-GGN-GGN-GGN-ACN, GGN-GGN-GGN-ACN-ACN-GGN-GGN, GGN-GGN-GGN-ACN-GGN-ACN-GGN, GGN-GGN-GGN-ACN-GGN-GGN-ACN, GGN-GGN-GGN-GGN-ACN-ACN-GGN, GGN-GGN-GGN-GGN-ACN-GGN-ACN- GGN-GGN-GGN-GGN-GGN-GGN-ACN, ACN-GGN-GGN-GGN-GGN-GGN-GGN, GGN-ACN-GGN-GGN-GGN-GGN-GGN, GGN-GGN-ACN-GGN-GGN-GGN-GGN, GGN-GGN-GGN-ACN-GGN-GGN-GGN, GGN-GGN-GGN-GGN-ACN-GGN-GGN, GGN-GGN-GGN-GGN-GGN-ACN-GGN

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TABLE 8

Symbol		Origin of designation
a	a	adenine
g	g	guanine
c	c	cytosine
t	t	thymine
u	u	uracil
r	g or a	purine
y	t/u or c	pyrimidine
m	a or c	amino
k	g or t/u	keto
s	g or c	strong interac tions 3H-bonds
w	a or t/u	weak interac tions 2H-bonds
b	g or c or t/u	not a
d	a or g or t/u	not c
h	a or c or t/u	not g
v	a or g or c	not t, not u
n	a or g or c or t/u, unknown, or other	any

TABLE 9

Code Construct	Admin Dose°	AUC_∞	T last	AUC/D	$t_{1/2}$	Cl	V_{ss}	MRT_∞	Dose normalized AUC_∞ §
	µg/kg	ng* h/mL	h	h*kg* ng/mL /µg	h	mL/h/ kg	mL/kg	h	ng* h/mL
NNT_{155}	2.6	274.5	24	105.6	6.2	9.5	78.2	8.2	316.7
C-GSF Control (A)	3.2	20.91	8	6.53	1.53	153.0	160.1	1.0	19.60
NEUPOGEN® 30	3.0	47.01	8	15.7	1.13	63.8	77.0	1.2	47.01
NEULASTA	6.0	116.4	24	19.4	3.04	51.5	266.1	5.2	58.20

1. A biologically active protein conjugate comprising a biologically active polypeptide coupled via a peptide bond to a polypeptide comprising from 2 to about 500 units of a peptide comprising as a major constituent, two or more residues of one amino acid selected from Gly (G), Asn (N) and Gln (Q), and as a minor constituent, one or more residues of one amino acid selected from Ala (A), Ser (S), Thr (T), Asp (D), Gln (Q), Glu (E), His (H) and Asn (N), provided that none of said amino acids is present in said major constituent and said minor constituent, such that said biologically active protein conjugate has a modified plasma half-life compared to the intrinsic half-life of the unconjugated biologically active polypeptide.

2. The protein conjugate of claim 1, wherein said peptide comprises 3-6 amino acid residues.

3. The protein conjugate of claim 1, wherein said peptide comprises 3 amino acid residues.

4. The protein conjugate of claim 1, wherein said peptide comprises 4 amino acid residues.

5. The protein conjugate of claim 1, wherein said peptide comprises 5 amino acid residues.

6. The protein conjugate of claim 5, wherein said minor constituent comprises 1 amino acid residue of said peptide.

7. The protein conjugate of claim 1, wherein said peptide comprises 6 amino acid residues.

8. The protein conjugate of claim 7, wherein said minor constituent comprises 1 amino acid residue of said peptide.

9. The protein conjugate of claim 1, wherein said peptide has a sequence consisting of N and T amino acid residues.

10. The protein conjugate of claim 1, wherein said peptide has a sequence consisting of N and E amino acid residues.

11. The protein conjugate of claim 1, wherein said peptide has a sequence consisting of Q and S amino acid residues.

12. The protein conjugate of claim 1, wherein said peptide has a sequence consisting of N and Q amino acid residues.

13. The protein conjugate of claim 1, wherein said polypeptide is N-terminal with respect to said biologically active polypeptide.

14. The protein conjugate of claim 1, wherein said polypeptide is C-terminal with respect to said biologically active polypeptide.

15. The protein conjugate of claim 1, wherein said polypeptide is situated at both the N and C-terminus with respect to said biologically active polypeptide.

16. The protein conjugate of claim 1, wherein said biologically active polypeptide is a cytokine.

17. The protein conjugate of claim 16, wherein said cytokine is granulocyte colony stimulating factor (G-CSF).

18. The protein conjugate of claim 16, wherein said cytokine is human growth hormone.

19. The protein conjugate of claim 16, wherein said cytokine is an interferon.

20. The protein conjugate of claim 19, wherein said interferon is a beta-interferon.

21. The protein conjugate of claim 19, wherein said interferon is a gamma-interferon.

22. The protein conjugate of claim 1, wherein said biologically active polypeptide comprises an antibody, antibody fragment, proteolytic antibody fragment or domain, single chain antibody, genetically or chemically optimized antibody or fragment thereof.

23. The protein conjugate of claim 1, wherein said biologically active polypeptide comprises a soluble gp120 or gp160 glycoprotein.

24. The protein conjugate of claim 1, wherein said biologically active polypeptide comprises a coagulation factor.

25. The protein conjugate of claim 1, wherein said biologically active polypeptide comprises a soluble receptor.

26. The protein conjugate of claim 25, wherein said soluble receptor comprises a tumor necrosis factor (TNF)-α type II receptor.

27. The protein conjugate of claim 1, wherein said biologically active polypeptide comprises erythropoietin.

28. The protein conjugate of claim 1, having a modified half-life that is decreased relative compared to the intrinsic half-life of the unconjugated biologically active polypeptide.

29. The protein conjugate of claim 28, wherein said biologically active polypeptide comprises a recombinant activated protein C.

30. The protein conjugate of claim 28, wherein said biologically active polypeptide comprises a recombinant Factor VII.

31. The protein conjugate of claim 1, wherein said biologically active polypeptide is a therapeutic enzyme.

32. A composition comprising the protein conjugate of claim 1 and a carrier.

33. The composition of claim 32, wherein said carrier is a pharmaceutically effective carrier.

34. A chimeric DNA molecule encoding the protein conjugate of claim 1.

35. A vector comprising the chimeric DNA molecule of claim 34.

36. The vector of claim 35, which is a plasmid.

37. The vector of claim 36, wherein said plasmid is pCE2.

38. A cell transformed with the vector of claim 35.

39. The cell of claim 38, which is a mammalian cell.

40. The cell of claim 39, wherein said mammalian cell is a Chinese hamster ovary (CHO) cell.

41. The cell of claim 38, which is a bacterium.

42. The cell of claim 41, wherein the bacterium is *E. coli*.

43. The cell of claim 38, which is yeast.

44. A method of making a biologically active protein conjugate comprising a biologically active polypeptide

coupled via peptide bond to a polypeptide comprising from 2 to about 500 units of a peptide comprising as a major constituent, two or more residues of one amino acid selected from Gly (G), Asn (N) and Gln (Q), and as a minor constituent, one or more residues of one amino acid selected from Ala (A), Ser (S), Thr (T), Asp (D), Gln (Q), Glu (E), His (H) and Asn (N), provided that none of said amino acids is present in said major constituent and said minor constituent, such that said biologically active protein has a modified plasma half-life compared to intrinsic half-life of the unconjugated biologically active polypeptide, said method comprising:

culturing a cell transformed with a chimeric DNA molecule encoding said protein conjugate under conditions whereby said DNA is expressed, thereby producing said protein conjugate; and

extracting an expression product of said chimeric DNA molecule from said cell.

45. The method of claim 44, wherein said chimeric DNA molecule is introduced into said cell through insertion of said chimeric DNA molecule into a vector which is then transformed into said cell.

46. A method of determining whether a given protein conjugate exhibits a modified plasma half-life compared to the intrinsic half-life of the unconjugated biologically active polypeptide, comprising:

a) preparing a protein conjugate comprising a biologically active polypeptide coupled via a peptide bond to a polypeptide that comprises from 2 to about 500 repeating units of a peptide motif, wherein the motif comprises a major constituent and a minor constituent, in which the major constituent comprises or consists of two or more residues of one amino acid selected from the group consisting of Gly (G), Asn (N) and Gln (Q), and the

minor constituent comprises or consists of one or more residues of one amino acid selected from the group consisting of Ala (A), Ser (S), Thr (T), Asp (D), Gln (Q), Glu (E), His (H) and Asn (N), wherein none of the amino acids is present in both the major constituent and said minor constituent, and

b) testing the protein conjugate to determine whether the protein conjugate has a modified plasma half-life compared to the intrinsic half-life of the unconjugated biologically active polypeptide.

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FIG. 1

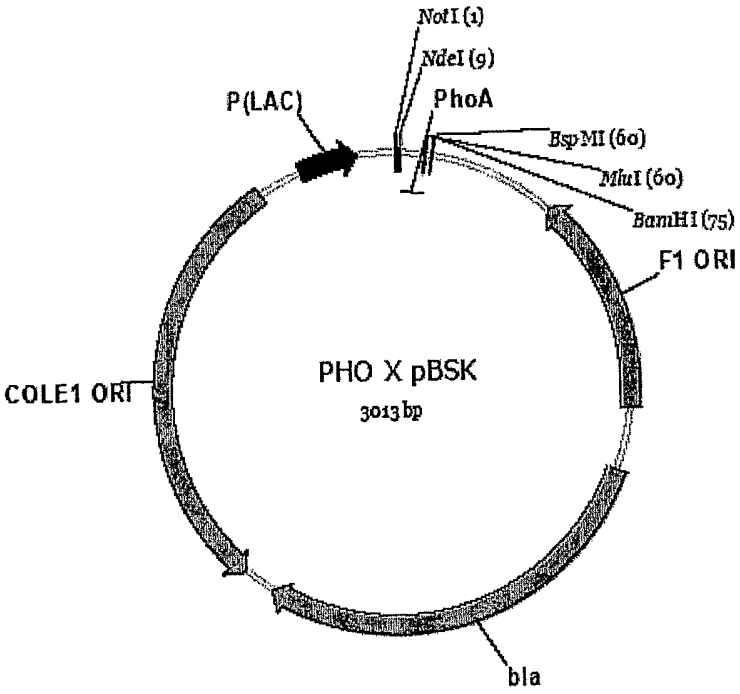
NotI (1)
NdeI (9)
PhoA
P(LAC)
BspMI (60)
MluI (60)
BamHI (75)
F1 ORI
PHO X pBSK
3013 bp
COLE1 ORI
bla

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FIG. 2

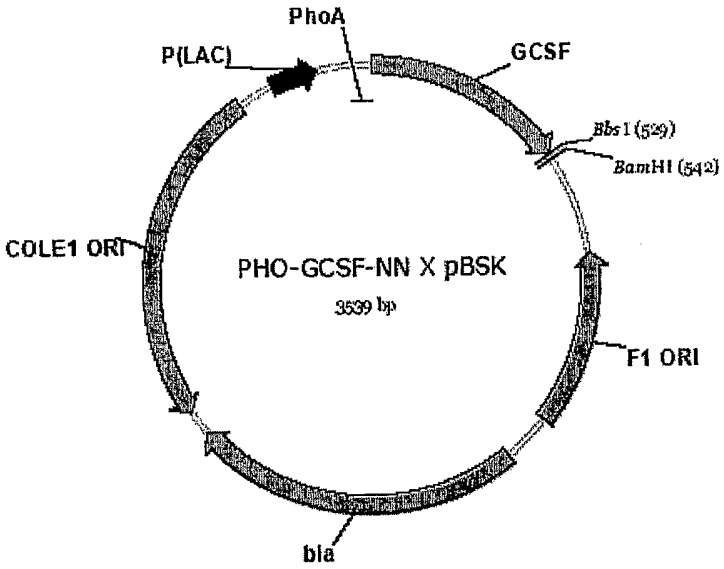
PhoA
P(LAC)
GCSF
Bbs I (529)
BamHI (542)
COLE1 ORI
PHO-GCSF-NN X pBSK
3539 bp
F1 ORI
bla

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FIG. 3

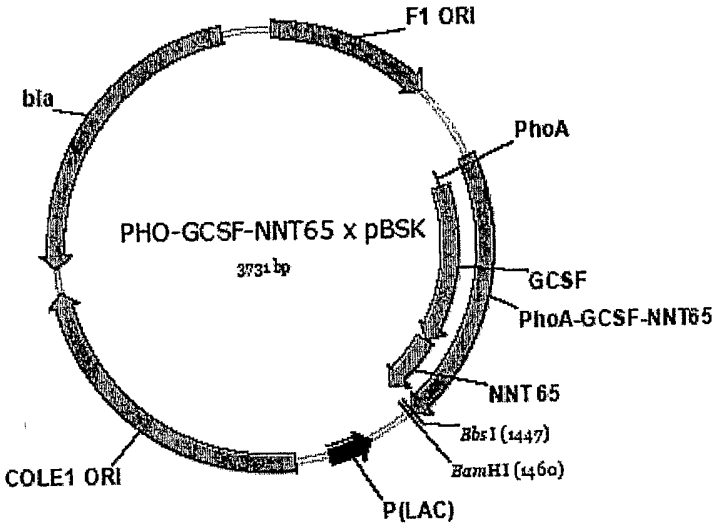
F1 ORI
bla
PhoA
PHO-GCSF-NNT65 x pBSK
3731 bp
GCSF
PhoA-GCSF-NNT65
NNT65
BbsI (1447)
BamHI (1460)
COLE1 ORI
P(LAC)

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FIG. 4

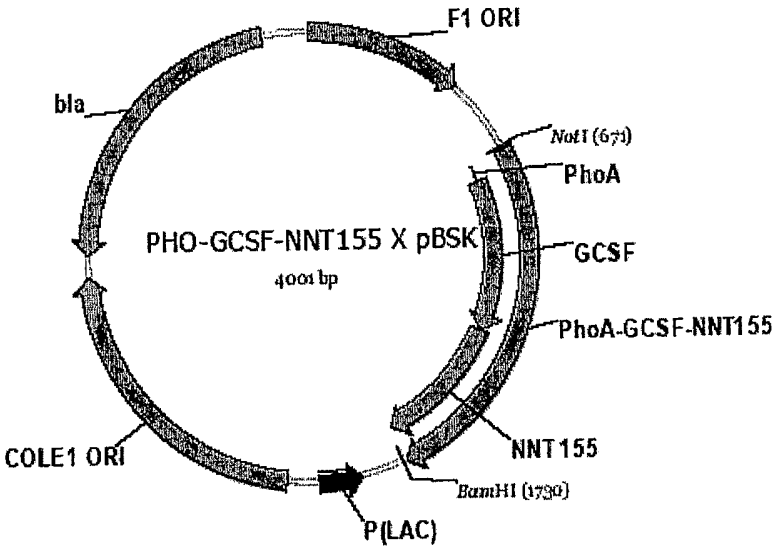
F1 ORI
bla
NotI (671)
PhoA
PHO-GCSF-NNT155 X pBSK
4001 bp
GCSF
PhoA-GCSF-NNT155
NNT155
COLE1 ORI
BamHI (1790)
P(LAC)

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FIG. 5

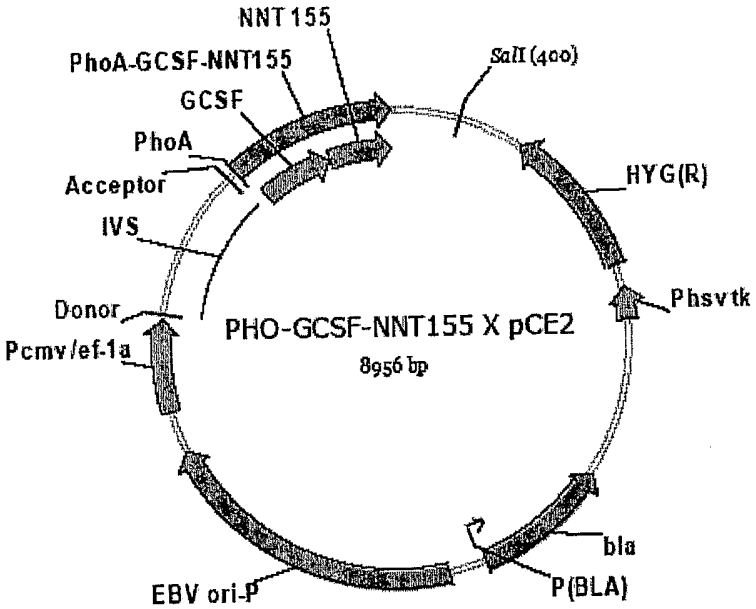
NNT155
PhoA-GCSF-NNT155
GCSF
PhoA
Acceptor
IVS
Donor
Pcmv/ef-1a
EBV ori-P
P(BLA)
bla
Phsvtk
HYG(R)
SalI (400)
PHO-GCSF-NNT155 X pCE2
8956 bp

FIG. 6

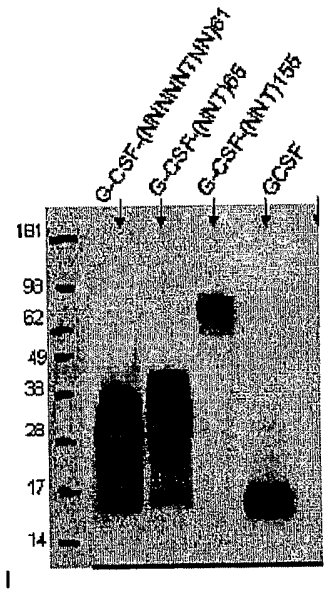
G-CSF-(NNNNNTNN)61
G-CSF-(NNT)66
G-CSF-(NNT)155
GCSF
181
98
62
49
38
28
17
14

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FIG. 7

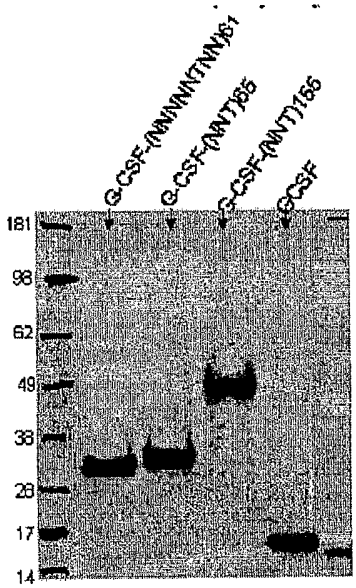
G-CSF-(NNNNNTNN)61
G-CSF-(NNT)85
G-CSF-(NNT)156
G-CSF
181
98
62
49
38
28
17
14

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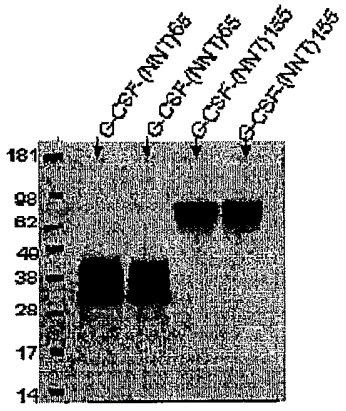
FIG. 8


G-CSF-(NNT)65
G-CSF-(NNT)65
G-CSF-(NNT)155
G-CSF-(NNT)155
181
98
62
49
38
28
17
14