

REPUBLIC OF SOUTH AFRICA
PATENTS ACT, 1978

(To be lodged in duplicate)

PUBLICATION PARTICULARS AND ABSTRACT
(Section 32(3)(a) - Regulations 22(1)(g) and 31)

REFERENCE : AP37363ZA00

OFFICIAL APPLICATION NO.	LODGING DATE	ACCEPTANCE DATE
2003/8513	22/23 31 October 2003	43 16-7-04

INTERNATIONAL CLASSIFICATION	NOT FOR PUBLICATION
51 C07K	CLASSIFIED BY :

FULL NAME(S) OF APPLICANT(S)

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EARLIEST PRIORITY CLAIMED	COUNTRY	NUMBER	DATE
NOTE : The country must be indicated by its International Abbreviation - see Schedule 4 of the Regulations.	33 US	60/290,196	11 May 2001
		31	32

TITLE OF INVENTION

54	PEPTIDES AND RELATED MOLECULES THAT BIND TO TALL-1
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57 ABSTRACT (NOT MORE THAN 150 WORDS)

NUMBER OF PAGES 330

FOR ABSTRACT SEE THE NEXT SHEET

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

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
21 November 2002 (21.11.2002)

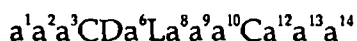
PCT

(10) International Publication Number
WO 02/092620 A2

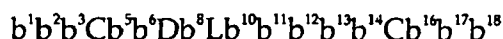
- (51) International Patent Classification: C07K (74) Agents: ODRE, Steven et al.; Amgen, Inc., One Amgen Center Drive, M/S 27-4-A, Thousand Oaks, CA 91320-1799 (US).
- (21) International Application Number: PCT/US02/15273
- (22) International Filing Date: 13 May 2002 (13.05.2002) (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 60/290,196 11 May 2001 (11.05.2001) US
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- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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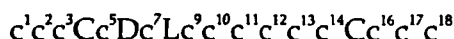
(54) Title: PEPTIDES AND RELATED MOLECULES THAT BIND TO TALL-1



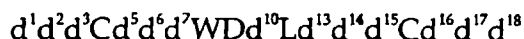
(SEQ. ID. NO: 100),



(SEQ. ID. NO: 104)



(SEQ. ID. NO: 105)



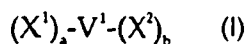
(SEQ. ID. NO: 106)



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(SEQ. ID NO: 109)



(57) Abstract: The present invention concerns therapeutic agents that modulate the activity of TALL-1. In accordance with the present invention, modulators of TALL-1 may comprise an amino acid sequence Dz^2Lz^4 wherein z^2 is an amino acid residue and z^4 is threonyl or isoleucyl. Exemplary molecules comprise a sequence of the formulae $a^1a^2a^3CDa^6La^8a^9a^{10}Ca^{12}a^{13}a^{14}$ (SEQ.ID.NO:100), $b^1b^2b^3Cb^5b^6Db^8Lb^{10}b^{11}b^{12}b^{13}b^{14}Cb^{16}b^{17}b^{18}$ (SEQ.ID.NO:104), $c^1c^2c^3Cc^5Dc^7Lc^9c^{10}c^{11}c^{12}c^{13}c^{14}Cc^{16}c^{17}c^{18}$ (SEQ.ID.NO:105), $d^1d^2d^3Cd^5d^6d^7WDd^{10}Ld^{13}d^{14}d^{15}Cd^{16}d^{17}d^{18}$ (SEQ.ID.NO:106), $e^1e^2e^3Ce^5e^6e^7De^9Le^{11}Ke^{13}Ce^{15}e^{16}e^{17}e^{18}$ (SEQ.ID.NO:107), $f^1f^2f^3Kf^5Df^7Lf^9Qf^{12}f^{13}f^{14}$ (SEQ.ID NO:109) wherein the substituents are as defined in the specification. The invention further comprises compositions of matter of the formula $(X^1)_s-V^1-(X^2)_b$ wherein V^1 is a vehicle that is covalently attached to one or more of the above TALL-1 modulating compositions of matter. The vehicle and the TALL-1 modulating composition of matter may be linked through the N- or C-terminus of the TALL-1 modulating portion. The preferred vehicle is an Fc domain, and the preferred Fc domain is an IgG Fc domain.



WO 02/092620 A2

PEPTIDES AND RELATED MOLECULES THAT BIND TO TALL-1

This application is related to U.S. provisional application no. 60/290,196,
5 filed May 11, 2001, which is hereby incorporated by reference.

Background of the Invention

After years of study in necrosis of tumors, tumor necrosis factors (TNFs) α and β were finally cloned in 1984. The ensuing years witnessed
10 the emergence of a superfamily of TNF cytokines, including fas ligand (FasL), CD27 ligand (CD27L), CD30 ligand (CD30L), CD40 ligand (CD40L), TNF-related apoptosis-inducing ligand (TRAIL, also designated AGP-1), osteoprotegerin binding protein (OPG-BP or OPG ligand), 4-1BB ligand, LIGHT, APRIL, and TALL-1. Smith *et al.* (1994), *Cell* 76: 959-962;
15 Lacey *et al.* (1998), *Cell* 93: 165-176; Chichepotiche *et al.* (1997), *J. Biol. Chem.* 272: 32401-32410; Mauri *et al.* (1998), *Immunity* 8: 21-30; Hahne *et al.* (1998), *J. Exp. Med.* 188: 1185-90; Shu *et al.* (1999), *J. Leukocyte Biology* 65: 680-3. This family is unified by its structure, particularly at the C-terminus. In addition, most members known to date are expressed in
20 immune compartments, although some members are also expressed in other tissues or organs, as well. Smith *et al.* (1994), *Cell* 76: 959-62. All ligand members, with the exception of LT- α , are type II transmembrane proteins, characterized by a conserved 150 amino acid region within C-terminal extracellular domain. Though restricted to only 20-25% identity,
25 the conserved 150 amino acid domain folds into a characteristic β -pleated sheet sandwich and trimerizes. This conserved region can be proteolytically released, thus generating a soluble functional form. Banner *et al.* (1993), *Cell* 73: 431-445.

Many members within this ligand family are expressed in lymphoid enriched tissues and play important roles in the immune system development and modulation. Smith *et al.* (1994). For example, TNF α is mainly synthesized by macrophages and is an important mediator for inflammatory responses and immune defenses. Tracey & Cerami (1994), *Ann. Rev. Med.* 45: 491-503. Fas-L, predominantly expressed in activated T cell, modulates TCR-mediated apoptosis of thymocytes. Nagata, S. & Suda, T. (1995) *Immunology Today* 16: 39-43; Castrim *et al.* (1996), *Immunity* 5: 617-27. CD40L, also expressed by activated T cells, provides an essential signal for B cell survival, proliferation and immunoglobulin isotype switching. Noelle (1996), *Immunity* 4: 415-9.

The cognate receptors for most of the TNF ligand family members have been identified. These receptors share characteristic multiple cysteine-rich repeats within their extracellular domains, and do not possess catalytic motifs within cytoplasmic regions. Smith *et al.* (1994). The receptors signal through direct interactions with death domain proteins (e.g. TRADD, FADD, and RIP) or with the TRAF proteins (e.g. TRAF2, TRAF3, TRAF5, and TRAF6), triggering divergent and overlapping signaling pathways, e.g. apoptosis, NF- κ B activation, or JNK activation. Wallach *et al.* (1999), *Annual Review of Immunology* 17: 331-67. These signaling events lead to cell death, proliferation, activation or differentiation. The expression profile of each receptor member varies. For example, TNFR1 is expressed on a broad spectrum of tissues and cells, whereas the cell surface receptor of OPGL is mainly restricted to the osteoclasts. Hsu *et al.* (1999) *Proc. Natl. Acad. Sci. USA* 96: 3540-5.

A number of research groups have recently identified TNF family ligands with the same or substantially similar sequence. The ligand has been variously named neutrokin α (WO 98/18921, published May 7, 1998), 63954 (WO 98/27114, published June 25, 1998), TL5 (EP 869 180, published October 7, 1998), NTN-2 (WO 98/55620 and WO 98/55621,

published December 10, 1998), TNRL1-alpha (WO 9911791, published March 11, 1999), kay ligand (WO99/12964, published March 18, 1999), and AGP-3 (U.S. Prov. App. Nos. 60/119,906, filed February 12, 1999 and 60/166,271, filed November 18, 1999, respectively); and TALL-1 (WO 00/68378, published Nov. 16, 2000). Each of these references is hereby incorporated by reference. Hereinafter, the ligands reported therein are collectively referred to as TALL-1.

TALL-1 is a member of the TNF ligand superfamily that is functionally involved in B cell survival and proliferation. Transgenic mice overexpressing TALL-1 had severe B cell hyperplasia and lupus-like autoimmune disease. Khare *et al.* (2000) PNAS 97(7):3370-3375). Both TACI and BCMA serve as cell surface receptors for TALL-1. Gross *et al.* (2000), Nature 404: 995-999; Ware (2000), J. Exp. Med. 192(11): F35-F37; Ware (2000), Nature 404: 949-950; Xia *et al.* (2000), J. Exp. Med. 192(1):137-143; Yu *et al.* (2000), Nature Immunology 1(3):252-256; Marsters *et al.* (2000), Current Biology 10:785-788; Hatzoglou *et al.* (2000) J. of Immunology 165:1322-1330; Shu *et al.* (2000) PNAS 97(16):9156-9161; Thompson *et al.* (2000) J. Exp. Med. 192(1):129-135; Mukhopadhyay *et al.* (1999) J. Biol. Chem. 274(23): 15978-81; Shu *et al.* (1999) J. Leukocyte Biol. 65:680-683; Gruss *et al.* (1995) Blood 85(12): 3378-3404; Smith *et al.* (1994), Cell 76: 959-962; U.S. Pat. No. 5,969,102, issued October 19, 1999; WO 00/67034, published November 9, 2000; WO 00/40716, published July 13, 2000; WO 99/35170, published July 15, 1999. Both receptors are expressed on B cells and signal through interaction with TRAF proteins. In addition, both TACI and BCMA also bind to another TNF ligand family member, APRIL. Yu *et al.* (2000), Nature Immunology 1(3) :252-256. APRIL has also been demonstrated to induce B cell proliferation.

To date, no recombinant or modified proteins employing peptide modulators of TALL-1 have been disclosed. Recombinant and modified

proteins are an emerging class of therapeutic agents. Useful modifications of protein therapeutic agents include combination with the "Fc" domain of an antibody and linkage to polymers such as polyethylene glycol (PEG) and dextran. Such modifications are discussed in detail in a patent
5 application entitled, "Modified Peptides as Therapeutic Agents,"
published WO 00/24782, which is hereby incorporated by reference in its entirety.

A much different approach to development of therapeutic agents is peptide library screening. The interaction of a protein ligand with its
10 receptor often takes place at a relatively large interface. However, as demonstrated for human growth hormone and its receptor, only a few key residues at the interface contribute to most of the binding energy.
Clackson et al. (1995), Science 267: 383-6. The bulk of the protein ligand merely displays the binding epitopes in the right topology or serves
15 functions unrelated to binding. Thus, molecules of only "peptide" length (2 to 40 amino acids) can bind to the receptor protein of a given large protein ligand. Such peptides may mimic the bioactivity of the large protein ligand ("peptide agonists") or, through competitive binding, inhibit the bioactivity of the large protein ligand ("peptide antagonists").

20 Phage display peptide libraries have emerged as a powerful method in identifying such peptide agonists and antagonists. See, for example, Scott et al. (1990), Science 249: 386; Devlin et al. (1990), Science 249: 404; U.S. Pat. No. 5,223,409, issued June 29, 1993; U.S. Pat. No. 5,733,731, issued March 31, 1998; U.S. Pat. No. 5,498,530, issued March 12,
25 1996; U.S. Pat. No. 5,432,018, issued July 11, 1995; U.S. Pat. No. 5,338,665, issued August 16, 1994; U.S. Pat. No. 5,922,545, issued July 13, 1999; WO 96/40987, published December 19, 1996; and WO 98/15833, published April 16, 1998 (each of which is incorporated by reference in its entirety).
In such libraries, random peptide sequences are displayed by fusion with

coat proteins of filamentous phage. Typically, the displayed peptides are affinity-eluted against an immobilized target protein. The retained phages may be enriched by successive rounds of affinity purification and repropagation. The best binding peptides may be sequenced to identify
5 key residues within one or more structurally related families of peptides. See, e.g., Cwirla *et al.* (1997), *Science* 276: 1696-9, in which two distinct families were identified. The peptide sequences may also suggest which residues may be safely replaced by alanine scanning or by mutagenesis at the DNA level. Mutagenesis libraries may be created and screened to
10 further optimize the sequence of the best binders. Lowman (1997), *Ann. Rev. Biophys. Biomol. Struct.* 26: 401-24.

Structural analysis of protein-protein interaction may also be used to suggest peptides that mimic the binding activity of large protein ligands. In such an analysis, the crystal structure may suggest the identity
15 and relative orientation of critical residues of the large protein ligand, from which a peptide may be designed. See, e.g., Takasaki *et al.* (1997), *Nature Biotech.* 15: 1266-70. These analytical methods may also be used to investigate the interaction between a receptor protein and peptides selected by phage display, which may suggest further modification of the
20 peptides to increase binding affinity.

Other methods compete with phage display in peptide research. A peptide library can be fused to the carboxyl terminus of the *lac* repressor and expressed in *E. coli*. Another *E. coli*-based method allows display on the cell's outer membrane by fusion with a peptidoglycan-associated
25 lipoprotein (PAL). Hereinafter, these and related methods are collectively referred to as "*E. coli* display." In another method, translation of random RNA is halted prior to ribosome release, resulting in a library of polypeptides with their associated RNA still attached. Hereinafter, this and related methods are collectively referred to as "ribosome display."

Other methods employ peptides linked to RNA; for example, PROfusion technology, Phylos, Inc. See, for example, Roberts & Szostak (1997), Proc. Natl. Acad. Sci. USA, 94: 12297-303. Hereinafter, this and related methods are collectively referred to as "RNA-peptide screening." Chemically

5 derived peptide libraries have been developed in which peptides are immobilized on stable, non-biological materials, such as polyethylene rods or solvent-permeable resins. Another chemically derived peptide library uses photolithography to scan peptides immobilized on glass slides. Hereinafter, these and related methods are collectively referred to as

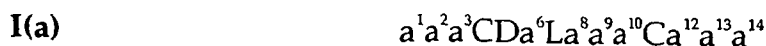
10 "chemical-peptide screening." Chemical-peptide screening may be advantageous in that it allows use of D-amino acids and other unnatural analogues, as well as non-peptide elements. Both biological and chemical methods are reviewed in Wells & Lowman (1992), Curr. Opin. Biotechnol. 3: 355-62. Conceptually, one may discover peptide mimetics of any

15 protein using phage display, RNA-peptide screening, and the other methods mentioned above.

Summary of the Invention

The present invention concerns therapeutic agents that modulate the activity of TALL-1. In accordance with the present invention,

20 modulators of TALL-1 may comprise an amino acid sequence Dz^2Lz^4 (SEQ ID NO: 108) wherein z^2 is an amino acid residue and z^4 is threonyl or isoleucyl. Such modulators of TALL-1 comprise molecules of the following formulae:



25 (SEQ. ID. NO: 100)

wherein:

a^1, a^2, a^3 are each independently absent or amino acid residues;

a^6 is an amino acid residue;

a^9 is a basic or hydrophobic residue;

30 a^8 is threonyl or isoleucyl;

a^{12} is a neutral polar residue; and
 a^{13} and a^{14} are each independently absent or amino acid residues.

I(b) $b^1 b^2 b^3 Cb^5 b^6 Db^8 Lb^{10} b^{11} b^{12} b^{13} b^{14} Cb^{16} b^{17} b^{18}$
 5 (SEQ. ID. NO: 104)

wherein:

b^1 and b^2 are each independently absent or amino acid residues;
 b^3 is an acidic or amide residue;
 b^5 is an amino acid residue;
 10 b^6 is an aromatic residue;
 b^8 is an amino acid residue;
 b^{10} is T or I;
 b^{11} is a basic residue;
 b^{12} and b^{13} are each independently amino acid residues;
 15 b^{14} is a neutral polar residue; and
 b^{16} , b^{17} , and b^{18} are each independently absent or amino acid residues.

I(c) $c^1 c^2 c^3 Cc^5 Dc^7 Lc^9 c^{10} c^{11} c^{12} c^{13} c^{14} Cc^{16} c^{17} c^{18}$
 (SEQ. ID. NO:105)

20 wherein:

c^1 , c^2 , and c^3 are each independently absent or amino acid residues;
 c^5 is an amino acid residue;
 c^7 is an amino acid residue;
 c^9 is T or I;
 25 c^{10} is a basic residue;
 c^{11} and c^{12} are each independently amino acid residues;
 c^{13} is a neutral polar residue;
 c^{14} is an amino acid residue;
 c^{16} is an amino acid residue;

c^{17} is a neutral polar residue; and

c^{18} is an amino acid residue or is absent.

I(d) $d^1 d^2 d^3 C d^5 d^6 d^7 W D d^{10} L d^{12} d^{13} d^{14} C d^{15} d^{16} d^{17}$

(SEQ. ID. NO: 106)

5 wherein:

d^1 , d^2 , and d^3 are each independently absent or amino acid residues;

d^5 , d^6 , and d^7 are each independently amino acid residues;

d^{10} is an amino acid residue;

d^{13} is T or I;

10 d^{14} is an amino acid residue; and

d^{16} , d^{17} , and d^{18} are each independently absent or amino acid residues.

I(e) $e^1 e^2 e^3 C e^5 e^6 e^7 D e^9 L e^{11} K e^{13} C e^{15} e^{16} e^{17} e^{18}$

(SEQ. ID. NO: 107)

15 wherein:

e^1 , e^2 , and e^3 are each independently absent or amino acid residues;

e^5 , e^6 , e^7 , e^9 , and e^{13} are each independently amino acid residues;

e^{11} is T or I; and

e^{15} , e^{16} , and e^{17} are each independently absent or amino acid residues.

20 **I(f)** $f^1 f^2 f^3 K f^5 D f^7 L f^9 f^{10} Q f^{12} f^{13} f^{14}$

(SEQ. ID NO: 109)

wherein:

f^1 , f^2 , and f^3 are absent or are amino acid residues (with one of f^1 , f^2 ,
and f^3 preferred to be C when one of f^{12} , f^{13} , and f^{14} is C);

25 f^5 is W, Y, or F (W preferred);

f^7 is an amino acid residue (L preferred);

f^9 is T or I (T preferred);

f^{10} is K, R, or H (K preferred);

f^{12} is C, a neutral polar residue, or a basic residue (W, C, or R preferred);

f^{13} is C, a neutral polar residue or is absent (V preferred); and

5 f^{14} is any amino acid residue or is absent;
provided that only one of f^1 , f^2 , and f^3 may be C, and only one of f^{12} , f^{13} , and f^{14} may be C.

Compounds of formulae I(a) through I(f) above incorporate Dz^2Lz^4 , as well as SEQ ID NO: 63 hereinafter. The sequence of I(f) was derived as
10 a consensus sequence as described in Example 1 hereinbelow. Of compounds within formula I(f), those within the formula

I(f) $f^1f^2f^3KWDFL^9KQf^{12}f^{13}f^{14}$
(SEQ ID NO: 125)

are preferred. Compounds falling within formula I(f) include SEQ ID
15 NOS: 32, 58, 60, 62, 63, 66, 67, 69, 70, 114, 115, 122, 123, 124, 147-150, 152-177, 179, 180, 187.

Also in accordance with the present invention are compounds having the consensus motif:

PFPWE
20 (SEQ ID NO: 110)

which also bind TALL-1.

Further in accordance with the present invention are compounds of the formulae:

I(g) $g^1g^2g^3Cg^5PFg^8Wg^{10}Cg^{11}g^{12}g^{13}$
25 (SEQ. ID. NO. 101)

wherein:

g^1 , g^2 and g^3 are each independently absent or amino acid residues;

g^5 is a neutral polar residue;

g^8 is a neutral polar residue;

30 g^{10} is an acidic residue;

g^{12} and g^{13} are each independently amino acid residues; and
 g^{14} is absent or is an amino acid residue.

I(h) $h^1 h^2 h^3 C W h^6 h^7 W G h^{10} C h^{12} h^{13} h^{14}$
 (SEQ. ID. NO: 102)

5 wherein:

h^1 , h^2 , and h^3 are each independently absent or amino acid residues;
 h^6 is a hydrophobic residue;
 h^7 is a hydrophobic residue;
 h^{10} is an acidic or polar hydrophobic residue; and
 10 h^{12} , h^{13} , and h^{14} are each independently absent or amino acid residues.

I(i) $i^{1,2,3} i^{5,6,7,8,9,10} i^{12,13,14}$
 (SEQ. ID. NO: 103)

wherein:

i^1 is absent or is an amino acid residue;
 15 i^2 is a neutral polar residue;
 i^3 is an amino acid residue;
 i^5 , i^6 , i^7 , and i^8 are each independently amino acid residues;
 i^9 is an acidic residue;
 i^{10} is an amino acid residue;
 20 i^{12} and i^{13} are each independently amino acid residues; and
 i^{14} is a neutral polar residue.

The compounds defined by formulae I(g) through I(i) also bind
 TALL-1.

Further in accordance with the present invention, modulators of
 25 TALL-1 comprise:

a) a TALL-1 modulating domain (e.g., an amino acid sequence
 of Formulae I(a) through I(i)), preferably the amino acid
 sequence Dz^2Lz^4 , or sequences derived therefrom by phage
 display, RNA-peptide screening, or the other techniques
 30 mentioned above; and

- b) a vehicle, such as a polymer (e.g., PEG or dextran) or an Fc domain, which is preferred;

wherein the vehicle is covalently attached to the TALL-1 modulating domain. The vehicle and the TALL-1 modulating domain may be linked through the N- or C-terminus of the TALL-1 modulating domain, as described further below. The preferred vehicle is an Fc domain, and the preferred Fc domain is an IgG Fc domain. Such Fc-linked peptides are referred to herein as "peptibodies." Preferred TALL-1 modulating domains comprise the amino acid sequences described hereinafter in Tables 1 and 2. Other TALL-1 modulating domains can be generated by phage display, RNA-peptide screening and the other techniques mentioned herein.

Further in accordance with the present invention is a process for making TALL-1 modulators, which comprises:

- a. selecting at least one peptide that binds to TALL-1 ; and
b. covalently linking said peptide to a vehicle.

The preferred vehicle is an Fc domain. Step (a) is preferably carried out by selection from the peptide sequences in Table 2 hereinafter or from phage display, RNA-peptide screening, or the other techniques mentioned herein.

The compounds of this invention may be prepared by standard synthetic methods, recombinant DNA techniques, or any other methods of preparing peptides and fusion proteins. Compounds of this invention that encompass non-peptide portions may be synthesized by standard organic chemistry reactions, in addition to standard peptide chemistry reactions when applicable.

The primary use contemplated for the compounds of this invention is as therapeutic or prophylactic agents. The vehicle-linked peptide may

have activity comparable to—or even greater than—the natural ligand mimicked by the peptide.

The compounds of this invention may be used for therapeutic or prophylactic purposes by formulating them with appropriate pharmaceutical carrier materials and administering an effective amount to a patient, such as a human (or other mammal) in need thereof. Other related aspects are also included in the instant invention.

Numerous additional aspects and advantages of the present invention will become apparent upon consideration of the figures and detailed description of the invention.

Brief Description of the Figures

Figure 1 shows exemplary Fc dimers that may be derived from an IgG1 antibody. "Fc" in the figure represents any of the Fc variants within the meaning of "Fc domain" herein. "X¹" and "X²" represent peptides or linker-peptide combinations as defined hereinafter. The specific dimers are as follows:

A, D: Single disulfide-bonded dimers. IgG1 antibodies typically have two disulfide bonds at the hinge region of the antibody. The Fc domain in Figures 1A and 1D may be formed by truncation between the two disulfide bond sites or by substitution of a cysteinyl residue with an unreactive residue (e.g., alanyl). In Figure 1A, the Fc domain is linked at the amino terminus of the peptides; in 1D, at the carboxyl terminus.

B, E: Doubly disulfide-bonded dimers. This Fc domain may be formed by truncation of the parent antibody to retain both cysteinyl residues in the Fc domain chains or by expression from a construct including a sequence encoding such an Fc domain. In Figure 1B, the Fc domain is linked at the amino terminus of the peptides; in 1E, at the carboxyl terminus.

C, F: Noncovalent dimers. This Fc domain may be formed by elimination of the cysteinyl residues by either truncation or substitution. One may desire to eliminate the cysteinyl residues to avoid impurities formed by reaction of the cysteinyl residue with cysteinyl residues of other proteins present in the host cell. The noncovalent bonding of the Fc domains is sufficient to hold together the dimer. Other dimers may be formed by using Fc domains derived from different types of antibodies (e.g., IgG2, IgM).

Figure 2 shows the structure of preferred compounds of the invention that feature tandem repeats of the pharmacologically active peptide. Figure 2A shows a single chain molecule and may also represent the DNA construct for the molecule. Figure 2B shows a dimer in which the linker-peptide portion is present on only one chain of the dimer. Figure 2C shows a dimer having the peptide portion on both chains. The dimer of Figure 2C will form spontaneously in certain host cells upon expression of a DNA construct encoding the single chain shown in Figure 3A. In other host cells, the cells could be placed in conditions favoring formation of dimers or the dimers can be formed in vitro.

Figure 3 shows exemplary nucleic acid and amino acid sequences (SEQ ID NOS: 1 and 2, respectively) of human IgG1 Fc that may be used in this invention.

Figures 4A through 4F show the nucleotide and amino acid sequences (SEQ ID NOS: 3-27) S of NdeI to SalI fragments encoding peptide and linker.

Figures 5A through 5M show the nucleotide sequence (SEQ ID NO: 28) of pAMG21-RANK-Fc vector, which was used to construct Fc-linked molecules of the present invention. These figures identify a number of features of the nucleic acid, including:

- promoter regions PcopB, PrepA, RNAI, APHII, luxPR, and luxPL;
- mRNA for APHII, luxR;

- coding sequences and amino acid sequences for the proteins copB protein, copT, repAI, repA4, APHII, luxR, RANK, and Fc;
- binding sites for the proteins copB, CRP;
- hairpins T1, T2, T7, and toop;
- 5 • operator site for lux protein;
- enzyme restriction sites for PfIII08I, BglII, ScaI, BmnI, DrdII, DraIII, BstBI, AceIII, AflII, PflMI, BglI, SfiI, BstEII, BspLulII, NspV, BpII, EagI, BcgI, NsiI, BsaI, Pspl406I, AatII, BsmI, NruI, NdeI, ApaLI, Acc65I, KpnI, SalI, AccI, BspEI, AhdI, BspHI, EconI, BsrGI, BmaI, SmaI, SexAI, BamHI, and BlpI.

10 Figures 6A and 6B show the DNA sequence (SEQ ID NO: 97) inserted into pCFM1656 between the unique AatII (position #4364 in pCFM1656) and SacII (position #4585 in pCFM1656) restriction sites to form expression plasmid pAMG21 (ATCC accession no. 98113).

Figure 7 shows that the TALL-1 peptibody (SEQ ID NO: 70) inhibits
 15 TALL-1-mediated B cell proliferation. Purified B cells (10^5) from B6 mice were cultured in triplicates in 96-well plated with the indicated amounts of TALL-1 consensus peptibody in the presence of 10 ng/ml TALL-1 plus 2 μ g/ml anti-IgM antibody. Proliferation was measured by radioactive [3 H]thymidine uptake in the last 18h of pulse. Data shown represent mean $\pm$ SD triplicate wells.

20 Figure 8 shows that a TALL-1 N-terminal tandem dimer peptibodies (SEQ ID NO: 123, 124 in Table 5B hereinafter) are preferable for inhibition of TALL-1-mediated B cell proliferation. Purified B cells (10^5) from B6 mice were cultured in triplicates in 96-well plated with the indicated amounts of TALL-1 12-3 peptibody and TALL-1 consensus peptibody (SEQ ID NOS: 115 and 122 of Table 5B) or the
 25 related dimer peptibodies (SEQ ID NOS: 123, 124) in the presence of 10 ng/ml TALL-1 plus 2 μ g/ml anti-IgM antibody. Proliferation was measured by radioactive [3 H]thymidine uptake in the last 18h of pulse. Data shown represent mean $\pm$ SD triplicate wells.

Figure 9. AGP3 peptibody binds to AGP3 with high affinity.
 30 Dissociation equilibrium constant (K_D) was obtained from nonlinear regression

of the competition curves using a dual-curve one-site homogeneous binding model (KinEx™ software). K_D is about 4 pM for AGP3 peptibody binding with human AGP3 (SEQ ID NO: 123).

Figures 10A and 10B. AGP3 peptibody blocks both human and murine AGP3 in the Biacore competition assay. Soluble human TACI protein was immobilized to B1 chip. 1 nM of recombinant human AGP3 protein (upper panel) or 5 nM of recombinant murine AGP3 protein (lower panel) was incubated with indicated amount of AGP3 peptibody before injected over the surface of receptor. Relative human AGP3 and murine AGP3 (binding response was shown (SEQ ID NO: 123).

Figures 11A and 11B. AGP3 peptibody blocked AGP3 binding to all three receptors TACI, BCMA and BAFFR in Biacore competition assay. Recombinant soluble receptor TACI, BCMA and BAFFR proteins were immobilized to CM5 chip. 1 nM of recombinant human AGP3 (upper panel) were incubated with indicated amount of AGP3 peptibody before injected over each receptor surface. Relative binding of AGP3 was measured. Similarly, 1 nM of recombinant APRIL protein was incubated with indicated amount of AGP3 peptibody before injected over each receptor surface. AGP3 peptibody didn't inhibit APRIL binding to all three receptors (SEQ ID NO: 123).

Figures 12A and 12B. AGP3 peptibody inhibits mouse serum immunoglobulin level increase induced by human AGP3 challenge. Balb/c mice received 7 daily intraperitoneal injections of 1 mg/Kg human AGP3 protein along with saline, human Fc, or AGP3 peptibody at indicated doses, and were bled on day 8. Serum total IgM and IgA level were measured by ELISA (SEQ ID NO: 123).

Figure 13. AGP3 peptibody treatment reduced arthritis severity in the mouse CIA model. Eight to 12 weeks old DBA/1 male mice were immunized with bovine collagen type II (bCII) emulsified in complete freunds adjuvant intradermally at the base of tail, and were boosted 3 weeks after the initial immunization with bCII emulsified in incomplete freunds adjuvant. Treatment with indicated dosage of AGP3 peptibody was begun from the day of booster

immunization for 4 weeks. As described before (Khare et al., *J. Immunol.* 155: 3653-9, 1995), all four paws were individually scored from 0-3 for arthritis severity (SEQ ID NO: 123).

Figure 14. AGP3 peptibody treatment inhibited anti-collagen antibody
5 generation in the mouse CIA model. Serum samples were taken one week after final treatment (day 35) as described above. Serum anti-collagen II antibody level was determined by ELISA analysis (SEQ ID NO: 123).

Figures 15A and 15B. AGP3 peptibody treatment delayed proteinuria onset and improved survival in NZB/NZW lupus mice. Five-month-old lupus
10 prone NZBx NZBWF1 mice were treated i.p. 3X/week for 8 weeks with PBS or indicated doses of AGP3 peptibody (SEQ ID NO: 123) or human Fc proteins. Protein in the urine was evaluated monthly throughout the life of the experiment with Albustix reagent strips (Bayer AG).

Figures 16A and 16B show the nucleic acid and amino acid
15 sequences of a preferred TALL-1-binding peptibody (SEQ ID NOS: 189 and 123)

Detailed Description of the Invention

Definition of Terms

20 The terms used throughout this specification are defined as follows, unless otherwise limited in specific instances.

General definitions

The term "comprising" means that a compound may include additional amino acids on either or both of the N- or C- termini of the
25 given sequence. Of course, these additional amino acids should not significantly interfere with the activity of the compound.

Additionally, physiologically acceptable salts of the compounds of this invention are also encompassed herein. The term "physiologically acceptable salts" refers to any salts that are known or later discovered to
30 be pharmaceutically acceptable. Some specific examples are: acetate;

trifluoroacetate; hydrohalides, such as hydrochloride and hydrobromide; sulfate; citrate; tartrate; glycolate; and oxalate.

Amino acids

The term "acidic residue" refers to amino acid residues in D- or L-form having sidechains comprising acidic groups. Exemplary acidic residues include D and E.

The term "amide residue" refers to amino acids in D- or L-form having sidechains comprising amide derivatives of acidic groups. Exemplary residues include N and Q.

The term "aromatic residue" refers to amino acid residues in D- or L-form having sidechains comprising aromatic groups. Exemplary aromatic residues include F, Y, and W.

The term "basic residue" refers to amino acid residues in D- or L-form having sidechains comprising basic groups. Exemplary basic residues include H, K, and R.

The term "hydrophilic residue" refers to amino acid residues in D- or L-form having sidechains comprising polar groups. Exemplary hydrophilic residues include C, S, T, N, and Q.

The term "nonfunctional residue" refers to amino acid residues in D- or L-form having sidechains that lack acidic, basic, or aromatic groups. Exemplary nonfunctional amino acid residues include M, G, A, V, I, L and norleucine (Nle).

The term "neutral polar residue" refers to amino acid residues in D- or L-form having sidechains that lack basic, acidic, or polar groups. Exemplary neutral polar amino acid residues include A, V, L, I, P, W, M, and F.

The term "polar hydrophobic residue" refers to amino acid residues in D- or L-form having sidechains comprising polar groups. Exemplary polar hydrophobic amino acid residues include T, G, S, Y, C, Q, and N.

The term "hydrophobic residue" refers to amino acid residues in D- or L-form having sidechains that lack basic or acidic groups. Exemplary hydrophobic amino acid residues include A, V, L, I, P, W, M, F, T, G, S, Y, C, Q, and N.

5 Peptides

The term "peptide" refers to molecules of 1 to 40 amino acids, with molecules of 5 to 20 amino acids preferred. Exemplary peptides may comprise the TALL-1 modulating domain of a naturally occurring molecule or comprise randomized sequences.

10 The term "randomized" as used to refer to peptide sequences refers to fully random sequences (e.g., selected by phage display methods or RNA-peptide screening) and sequences in which one or more residues of a naturally occurring molecule is replaced by an amino acid residue not appearing in that position in the naturally occurring molecule. Exemplary
15 methods for identifying peptide sequences include phage display, *E. coli* display, ribosome display, RNA-peptide screening, chemical screening, and the like.

The term "TALL-1 modulating domain" refers to any amino acid sequence that binds to the TALL-1 and comprises naturally occurring
20 sequences or randomized sequences. Exemplary TALL-1 modulating domains can be identified or derived by phage display or other methods mentioned herein.

The term "TALL-1 antagonist" refers to a molecule that binds to the TALL-1 and increases or decreases one or more assay parameters opposite
25 from the effect on those parameters by full length native TALL-1. Such activity can be determined, for example, by such assays as described in the subsection entitled "Biological activity of AGP-3" in the Materials & Methods section of the patent application entitled, "TNF-RELATED PROTEINS", WO 00/47740, published August 17, 2000.

Vehicles and peptibodies

The term "vehicle" refers to a molecule that prevents degradation
5 and/or increases half-life, reduces toxicity, reduces immunogenicity, or
increases biological activity of a therapeutic protein. Exemplary vehicles
include an Fc domain (which is preferred) as well as a linear polymer (e.g.,
polyethylene glycol (PEG), polylysine, dextran, etc.); a branched-chain
polymer (see, for example, U.S. Patent No. 4,289,872 to Denkenwalter et
10 al., issued September 15, 1981; 5,229,490 to Tam, issued July 20, 1993; WO
93/21259 by Frechet et al., published 28 October 1993); a lipid; a
cholesterol group (such as a steroid); a carbohydrate or oligosaccharide
(e.g., dextran); any natural or synthetic protein, polypeptide or peptide
that binds to a salvage receptor; albumin, including human serum
15 albumin (HSA), leucine zipper domain, and other such proteins and
protein fragments. Vehicles are further described hereinafter.

The term "native Fc" refers to molecule or sequence comprising the
sequence of a non-antigen-binding fragment resulting from digestion of
whole antibody, whether in monomeric or multimeric form. The original
20 immunoglobulin source of the native Fc is preferably of human origin and
may be any of the immunoglobulins, although IgG1 and IgG2 are
preferred. Native Fc's are made up of monomeric polypeptides that may
be linked into dimeric or multimeric forms by covalent (i.e., disulfide
bonds) and non-covalent association. The number of intermolecular
25 disulfide bonds between monomeric subunits of native Fc molecules
ranges from 1 to 4 depending on class (e.g., IgG, IgA, IgE) or subclass (e.g.,
IgG1, IgG2, IgG3, IgA1, IgGA2). One example of a native Fc is a disulfide-
bonded dimer resulting from papain digestion of an IgG (see Ellison et al.

(1982), Nucleic Acids Res. 10: 4071-9). The term "native Fc" as used herein is generic to the monomeric, dimeric, and multimeric forms.

The term "Fc variant" refers to a molecule or sequence that is modified from a native Fc but still comprises a binding site for the salvage
5 receptor, FcRn. International applications WO 97/34631 (published 25 September 1997) and WO 96/32478 describe exemplary Fc variants, as well as interaction with the salvage receptor, and are hereby incorporated by reference in their entirety. Thus, the term "Fc variant" comprises a molecule or sequence that is humanized from a non-human native Fc.
10 Furthermore, a native Fc comprises sites that may be removed because they provide structural features or biological activity that are not required for the fusion molecules of the present invention. Thus, the term "Fc variant" comprises a molecule or sequence that lacks one or more native Fc sites or residues that affect or are involved in (1) disulfide bond
15 formation, (2) incompatibility with a selected host cell (3) N-terminal heterogeneity upon expression in a selected host cell, (4) glycosylation, (5) interaction with complement, (6) binding to an Fc receptor other than a salvage receptor, or (7) antibody-dependent cellular cytotoxicity (ADCC). Fc variants are described in further detail hereinafter.

20 The term "Fc domain" encompasses native Fc and Fc variant molecules and sequences as defined above. As with Fc variants and native Fc's, the term "Fc domain" includes molecules in monomeric or multimeric form, whether digested from whole antibody or produced by other means.

25 The term "multimer" as applied to Fc domains or molecules comprising Fc domains refers to molecules having two or more polypeptide chains associated covalently, noncovalently, or by both covalent and non-covalent interactions. IgG molecules typically form dimers; IgM, pentamers; IgD, dimers; and IgA, monomers, dimers,

trimers, or tetramers. Multimers may be formed by exploiting the sequence and resulting activity of the native Ig source of the Fc or by derivatizing (as defined below) such a native Fc.

The term "dimer" as applied to Fc domains or molecules comprising Fc domains refers to molecules having two polypeptide chains associated covalently or non-covalently. Thus, exemplary dimers within the scope of this invention are as shown in Figure 1.

The terms "derivatizing" and "derivative" or "derivatized" comprise processes and resulting compounds respectively in which (1) the compound has a cyclic portion; for example, cross-linking between cysteinyl residues within the compound; (2) the compound is cross-linked or has a cross-linking site; for example, the compound has a cysteinyl residue and thus forms cross-linked dimers in culture or *in vivo*; (3) one or more peptidyl linkage is replaced by a non-peptidyl linkage; (4) the N-terminus is replaced by $-NRR^1$, $-NRC(O)R^1$, $-NRC(O)OR^1$, $-NRS(O)_2R^1$, $-NHC(O)NHR$, a succinimide group, or substituted or unsubstituted benzyloxycarbonyl-NH-, wherein R and R^1 and the ring substituents are as defined hereinafter; (5) the C-terminus is replaced by $-C(O)R^2$ or $-NR^3R^4$ wherein R^2 , R^3 and R^4 are as defined hereinafter; and (6) compounds in which individual amino acid moieties are modified through treatment with agents capable of reacting with selected side chains or terminal residues. Derivatives are further described hereinafter.

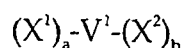
The terms "peptibody" and "peptibodies" refer to molecules comprising an Fc domain and at least one peptide. Such peptibodies may be multimers or dimers or fragments thereof, and they may be derivatized. In the present invention, the molecules of formulae II through VI hereinafter are peptibodies when V^1 is an Fc domain.

Structure of compounds

In General. The present inventors identified sequences capable of binding to and modulating the biological activity of TALL-1. These sequences can be modified through the techniques mentioned above
 5 by which one or more amino acids may be changed while maintaining or even improving the binding affinity of the peptide.

In the compositions of matter prepared in accordance with this invention, the peptide(s) may be attached to the vehicle through the peptide's N-terminus or C-terminus. Any of these peptides may be linked
 10 in tandem (i.e., sequentially), with or without linkers. Thus, the vehicle-peptide molecules of this invention may be described by the following formula:

II



15 wherein:

V^1 is a vehicle (preferably an Fc domain);

X^1 and X^2 are each independently selected from $-(L^1)_c-P^1$, $-(L^1)_c-P^1-(L^2)_d-P^2$, $-(L^1)_c-P^1-(L^2)_d-P^2-(L^3)_e-P^3$, and $-(L^1)_c-P^1-(L^2)_d-P^2-(L^3)_e-P^3-(L^4)_f-P^4$

P^1 , P^2 , P^3 , and P^4 are each independently sequences of TALL-1
 20 modulating domains, such as those of Formulae I(a) through I(i);

L^1 , L^2 , L^3 , and L^4 are each independently linkers; and

a , b , c , d , e , and f are each independently 0 or 1, provided that at least one of a and b is 1.

Thus, compound II comprises preferred compounds of the
 25 formulae

III



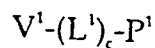
and multimers thereof wherein V^1 is an Fc domain and is attached at the C-terminus of A^1 ;

IV



and multimers thereof wherein V^1 is an Fc domain and is attached at the N-terminus of A^2 ;

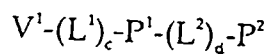
5 V



and multimers thereof wherein V^1 is an Fc domain and is attached at the N-terminus of $-(L^1)_c-P^1$; and

VI

10



and multimers thereof wherein V^1 is an Fc domain and is attached at the N-terminus of $-L^1-P^1-L^2-P^2$.

Peptides. The peptides of this invention are useful as TALL-1 modulating peptides or as TALL-1 modulating domains in the molecules of formulae II through VI. Molecules of this invention comprising these peptide sequences may be prepared by methods known in the art.

Preferred peptide sequences are those of the foregoing formulae I(a) having the substituents identified below.

Table 1--Preferred peptide substituents

Formula I(a)	a⁸ is T; a⁹ is a basic residue (K most preferred); and a¹² is a neutral polar residue (F most preferred).
Formula I(b)	b³ is D, Q, or E; b⁶ is W or Y; b¹⁰ is T; b¹¹ is K or R; and b¹⁴ is V or L.
Formula I(c)	c⁹ is T ; c¹⁰ is K or R; c¹³ is a I, L, or V; and c¹⁷ is A or L.
Formula I(d)	d ¹³ is T.
Formula I(e)	e ¹¹ is T.
Formula I(f)	[f⁶]f⁹ is T; f⁷ is K; and f¹⁰ is V.
Formula I(g)	g⁵ is W; g⁸ is P; g¹⁰ is E; and g¹³ is a basic residue.
Formula I(h)	h¹ is G; h⁶ is A; h⁷ is a neutral polar residue; and h¹⁰ is an acidic residue.
Formula I(i)	i² is W; and i¹⁴ is W.

Table 2—Preferred TALL-1 modulating domains

Sequence	SEQ ID NO:
PGTCFPFPWECTHA	29
WGACWFPFWECFKE	30
VPFCDLLTKHCFEA	31
GSRCYKWDVLTQCFHH	32
LPGCKWDLLIKQWCDPL	33
SADCYFDILTKSDVCTSS	34
SDDCMYDQLTRMFICSNL	35
DLNCKYDELTYKEWCQFN	36
FHDCKYDILLTRQMVCHGL	37
RNHCFWDHLLKQDICPSP	38
ANQCWWDSLTKKNVCEFF	39
YKGRQWMDILTRSWVSL	126
QDVGLWWDILTRAWMPNI	127
QNAQRVWDLIRTWVYPQ	128
GWNEAWWDELTKIWVLEQ	129
RITCDTWDSLKKCVPOS	130
GAIMQFWDSLTKTWLRQS	131
WLHSGWWDPLTKHWLQKV	132
SEWFFWFDPLTRAQLKFR	133
GVWFWWFDPLTKQWTQAG	134
MQCKGYDILTKWCVTNG	135
LWSKEVWDILTKSWVSQA	136
KAAGWWFDWLTKVWPAP	137
AYQTWFWDSLTRLWLSTT	138
SGQHFWWDLLTRSWTPST	139
LGVGQKWDPPLTKQVSRG	140
VGKMCQWDPLIKRTVCVG	141
CRQGAKFDDLTKQCLLGR	142
GQAIRHWDVLTQWVDSQ	143
RGPCGSWDLCLKHCLDSQ	144
WQWKQWDLCLKQMVWVG	145
PITICRKDLCLKQVVCLD	146
KTCNGKWDLCLKQCLQQA	147
KCLKGKWDLCLKQCVTEV	148
RCWNGKWDLCLKQCIHPW	149
NRDMRKWDPLIKQWIVRP	150
QAAAATWDLCLKQWLVP	151
PEGGPKWDPLTKQFLPPV	152
QTPQKKWDLCLKQWFTRN	153
IGSPCKWDLCLKQMICQT	154
CTAAGKWDLCLKQCIQEK	155
VSQCMKWDLCLKQCLQGW	156
VWGTWKWDLCLKQYLPPQ	157
GWWEMKWDLCLKQWYRPO	158
TAQVSKWDLCLKQWLPLA	159
QLWGTKWDLCLKQYIQIM	160
WATSQKWDLCLKQWVQNM	161
QRQCAKWDLCLKQCVLFY	162

KTTCCKWDLTKQRICQV	163
LLCQGWDLTKQCLKLR	164
LMWFWKDLTKQLVPTF	165
QTWAWKDLTKQWIGPM	166
NKELLKDLTKQCRGRS	167
GQKDLKDLTKQYVRQS	168
PKPCQKDLTKQCLGSV	169
GQIGWKDLTKQWIQTR	170
VWLDWKDLTKQWIHPQ	171
QEWYKDLTKQWGWLR	172
HWDSWKDLTKQWVQA	173
TRPLQKDLTKQWLRVG	174
SDQWQKDLTKQWFDV	175
QQTFMKDLTKQWIRRH	176
QGECKDLTKQCFPGQ	177
GQMGWRWDPLIKMCLGPS	178
QLDGCKDLTKQKVCIP	179
HGYWQKDLTKQWSSE	180
HQQCGWDLTRIYLPCH	181
LHKACKDLTKQCWPMQ	182
GPPGSVDLTKIWIQTG	183
ITQDWRFDTLTRLWPLR	184
QGGFAAWDLTKMWITVP	185
GHGTPWWDALTRIWLGV	186
VWPWQKDLTKQFVFQD	187
WQWSWKDLTKROYISS	188
NQTLWKDLTKQFITYM	60
PVYQGWDTLTKLYIWDG	61
WLDGGWRDPLIKRSVQLG	62
GHQQFKDLTKQWVQSN	63
QRVGQFWDVLTKMFITGS	64
QAQGWSYDALIKTWIRWP	65
GWMHWKWDPLTKQALPWM	66
GHPTYKDLTKQWILQM	67
WNNWSLWDPLTKLWLQQN	68
WQWGWKDLTKQWVQQQ	69
GQMGWRWDPLTKMWLGTS	70

It is noted that the known receptors for TALL-1 bear some sequence homology with preferred peptides:

12-3 LPGAKWDLLIKQWVCDPL

5 **BAFFR** MRRGPRSLGRDAPVPTPCVPTECYDLLVRKCVDCRLL

TACI TICNHQSQRTCAAFCRSLSCRKEQGKFYDHLLRDCISCASI

BCMA FVSPSQEIRGRFRMLQMAGQCSQNEYFDSSLHACIPCQLRC

(SEQ ID NOS: 33, 195, 196, and 197, respectively).

Any peptide containing a cysteinyl residue may be cross-linked with
10 another Cys-containing peptide, either or both of which may be linked to a

vehicle. Any peptide having more than one Cys residue may form an intrapeptide disulfide bond, as well. Any of these peptides may be derivatized as described hereinafter.

Additional useful peptide sequences may result from conservative
5 and/or non-conservative modifications of the amino acid sequences of the sequences in Table 2.

Conservative modifications will produce peptides having functional and chemical characteristics similar to those of the peptide from which such modifications are made. In contrast, substantial modifications
10 in the functional and/or chemical characteristics of the peptides may be accomplished by selecting substitutions in the amino acid sequence that differ significantly in their effect on maintaining (a) the structure of the molecular backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule
15 at the target site, or (c) the size of the molecule.

For example, a "conservative amino acid substitution" may involve a substitution of a native amino acid residue with a nonnative residue such that there is little or no effect on the polarity or charge of the amino acid residue at that position. Furthermore, any native residue in the
20 polypeptide may also be substituted with alanine, as has been previously described for "alanine scanning mutagenesis" (see, for example, MacLennan et al., 1998, Acta Physiol. Scand. Suppl. 643:55-67; Sasaki et al., 1998, Adv. Biophys. 35:1-24, which discuss alanine scanning mutagenesis).

Desired amino acid substitutions (whether conservative or non-
25 conservative) can be determined by those skilled in the art at the time such substitutions are desired. For example, amino acid substitutions can be used to identify important residues of the peptide sequence, or to increase or decrease the affinity of the peptide or vehicle-peptide molecules (see preceding formulae) described herein. Exemplary amino acid
30 substitutions are set forth in Table 3.

Table 3—Amino Acid Substitutions

Original Residues	Exemplary Substitutions	Preferred Substitutions
Ala (A)	Val, Leu, Ile	Val
Arg (R)	Lys, Gln, Asn	Lys
Asn (N)	Gln	Gln
Asp (D)	Glu	Glu
Cys (C)	Ser, Ala	Ser
Gln (Q)	Asn	Asn
Glu (E)	Asp	Asp
Gly (G)	Pro, Ala	Ala
His (H)	Asn, Gln, Lys, Arg	Arg
Ile (I)	Leu, Val, Met, Ala, Phe, Norleucine	Leu
Leu (L)	Norleucine, Ile, Val, Met, Ala, Phe	Ile
Lys (K)	Arg, 1,4 Diamino-butyrac Acid, Gln, Asn	Arg
Met (M)	Leu, Phe, Ile	Leu
Phe (F)	Leu, Val, Ile, Ala, Tyr	Leu
Pro (P)	Ala	Gly
Ser (S)	Thr, Ala, Cys	Thr
Thr (T)	Ser	Ser
Trp (W)	Tyr, Phe	Tyr
Tyr (Y)	Trp, Phe, Thr, Ser	Phe
Val (V)	Ile, Met, Leu, Phe, Ala, Norleucine	Leu

5 In certain embodiments, conservative amino acid substitutions also encompass non-naturally occurring amino acid residues which are

typically incorporated by chemical peptide synthesis rather than by synthesis in biological systems.

As noted in the foregoing section "Definition of Terms," naturally occurring residues may be divided into classes based on common
5 sidechain properties that may be useful for modifications of sequence. For example, non-conservative substitutions may involve the exchange of a member of one of these classes for a member from another class. Such substituted residues may be introduced into regions of the peptide that are homologous with non-human orthologs, or into the non-homologous
10 regions of the molecule. In addition, one may also make modifications using P or G for the purpose of influencing chain orientation.

In making such modifications, the hydropathic index of amino acids may be considered. Each amino acid has been assigned a hydropathic index on the basis of their hydrophobicity and charge
15 characteristics, these are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (-0.4); threonine (-0.7); serine (-0.8); tryptophan (-0.9); tyrosine (-1.3); proline (-1.6); histidine (-3.2); glutamate (-3.5); glutamine (-3.5); aspartate (-3.5); asparagine (-3.5); lysine (-3.9); and arginine (-4.5).

20 The importance of the hydropathic amino acid index in conferring interactive biological function on a protein is understood in the art. Kyte et al., *J. Mol. Biol.*, 157: 105-131 (1982). It is known that certain amino acids may be substituted for other amino acids having a similar hydropathic index or score and still retain a similar biological activity. In making
25 changes based upon the hydropathic index, the substitution of amino acids whose hydropathic indices are within ± 2 is preferred, those which are within ± 1 are particularly preferred, and those within ± 0.5 are even more particularly preferred.

It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity. The greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with its immunogenicity and antigenicity, i.e., with a biological property of the protein.

The following hydrophilicity values have been assigned to amino acid residues: arginine (+3.0); lysine (+3.0); aspartate (+3.0 $\pm$ 1); glutamate (+3.0 $\pm$ 1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (-0.4); proline (-0.5 $\pm$ 1); alanine (-0.5); histidine (-0.5); cysteine (-1.0); methionine (-1.3); valine (-1.5); leucine (-1.8); isoleucine (-1.8); tyrosine (-2.3); phenylalanine (-2.5); tryptophan (-3.4). In making changes based upon similar hydrophilicity values, the substitution of amino acids whose hydrophilicity values are within ± 2 is preferred, those which are within ± 1 are particularly preferred, and those within ± 0.5 are even more particularly preferred. One may also identify epitopes from primary amino acid sequences on the basis of hydrophilicity. These regions are also referred to as "epitopic core regions."

A skilled artisan will be able to determine suitable variants of the polypeptide as set forth in the foregoing sequences using well known techniques. For identifying suitable areas of the molecule that may be changed without destroying activity, one skilled in the art may target areas not believed to be important for activity. For example, when similar polypeptides with similar activities from the same species or from other species are known, one skilled in the art may compare the amino acid sequence of a peptide to similar peptides. With such a comparison, one can identify residues and portions of the molecules that are conserved among similar polypeptides. It will be appreciated that changes in areas of a peptide that are not conserved relative to such similar peptides would

be less likely to adversely affect the biological activity and/or structure of the peptide. One skilled in the art would also know that, even in relatively conserved regions, one may substitute chemically similar amino acids for the naturally occurring residues while retaining activity (conservative amino acid residue substitutions). Therefore, even areas that may be important for biological activity or for structure may be subject to conservative amino acid substitutions without destroying the biological activity or without adversely affecting the peptide structure.

Additionally, one skilled in the art can review structure-function studies identifying residues in similar peptides that are important for activity or structure. In view of such a comparison, one can predict the importance of amino acid residues in a peptide that correspond to amino acid residues that are important for activity or structure in similar peptides. One skilled in the art may opt for chemically similar amino acid substitutions for such predicted important amino acid residues of the peptides.

One skilled in the art can also analyze the three-dimensional structure and amino acid sequence in relation to that structure in similar polypeptides. In view of that information, one skilled in the art may predict the alignment of amino acid residues of a peptide with respect to its three dimensional structure. One skilled in the art may choose not to make radical changes to amino acid residues predicted to be on the surface of the protein, since such residues may be involved in important interactions with other molecules. Moreover, one skilled in the art may generate test variants containing a single amino acid substitution at each desired amino acid residue. The variants can then be screened using activity assays known to those skilled in the art. Such data could be used to gather information about suitable variants. For example, if one discovered that a change to a particular amino acid residue resulted in destroyed,

undesirably reduced, or unsuitable activity, variants with such a change would be avoided. In other words, based on information gathered from such routine experiments, one skilled in the art can readily determine the amino acids where further substitutions should be avoided either alone or
5 in combination with other mutations.

A number of scientific publications have been devoted to the prediction of secondary structure. See Moult J., Curr. Op. in Biotech., 7(4): 422-427 (1996), Chou et al., Biochemistry, 13(2): 222-245 (1974); Chou et al., Biochemistry, 113(2): 211-222 (1974); Chou et al., Adv. Enzymol. Relat.
10 Areas Mol. Biol., 47: 45-148 (1978); Chou et al., Ann. Rev. Biochem., 47: 251-276 and Chou et al., Biophys. J., 26: 367-384 (1979). Moreover, computer programs are currently available to assist with predicting secondary structure. One method of predicting secondary structure is based upon homology modeling. For example, two polypeptides or
15 proteins which have a sequence identity of greater than 30%, or similarity greater than 40% often have similar structural topologies. The recent growth of the protein structural data base (PDB) has provided enhanced predictability of secondary structure, including the potential number of folds within a polypeptide's or protein's structure. See Holm et al., Nucl.
20 Acid. Res., 27(1): 244-247 (1999). It has been suggested (Brenner et al., Curr. Op. Struct. Biol., 7(3): 369-376 (1997)) that there are a limited number of folds in a given polypeptide or protein and that once a critical number of structures have been resolved, structural prediction will gain dramatically in accuracy.

25 Additional methods of predicting secondary structure include "threading" (Jones, D., Curr. Opin. Struct. Biol., 7(3): 377-87 (1997); Sippl et al., Structure, 4(1): 15-9 (1996)), "profile analysis" (Bowie et al., Science, 253: 164-170 (1991); Gribskov et al., Meth. Enzym., 183: 146-159 (1990);

Gribskov *et al.*, *Proc. Nat. Acad. Sci.*, 84(13): 4355-8 (1987)), and “evolutionary linkage” (See Home, *supra*, and Brenner, *supra*).

Vehicles. This invention requires the presence of at least one vehicle (V¹) attached to a peptide through the N-terminus, C-terminus or a
5 sidechain of one of the amino acid residues. Multiple vehicles may also be used; e.g., Fc’s at each terminus or an Fc at a terminus and a PEG group at the other terminus or a sidechain. Exemplary vehicles include:

- an Fc domain;
- other proteins, polypeptides, or peptides capable of binding to a
10 salvage receptor;
- human serum albumin (HSA);
- a leucine zipper (LZ) domain;
- polyethylene glycol (PEG), including 5 kD, 20 kD, and 30 kD PEG, as well as other polymers;
- 15 • dextran;

and other molecules known in the art to provide extended half-life and/or protection from proteolytic degradation or clearance.

An Fc domain is the preferred vehicle. The Fc domain may be fused to the N or C termini of the peptides or at both the N and C termini.

20 Fusion to the N terminus is preferred.

As noted above, Fc variants are suitable vehicles within the scope of this invention. A native Fc may be extensively modified to form an Fc variant in accordance with this invention, provided binding to the salvage receptor is maintained; see, for example WO 97/34631 and WO 96/32478.

25 In such Fc variants, one may remove one or more sites of a native Fc that provide structural features or functional activity not required by the fusion molecules of this invention. One may remove these sites by, for example, substituting or deleting residues, inserting residues into the site, or truncating portions containing the site. The inserted or substituted

residues may also be altered amino acids, such as peptidomimetics or D-amino acids. Fc variants may be desirable for a number of reasons, several of which are described below. Exemplary Fc variants include molecules and sequences in which:

- 5 1. Sites involved in disulfide bond formation are removed. Such removal may avoid reaction with other cysteine-containing proteins present in the host cell used to produce the molecules of the invention. For this purpose, the cysteine-containing segment at the N-terminus may be truncated or cysteine residues may be deleted or substituted with other
10 amino acids (e.g., alanyl, seryl). In particular, one may truncate the N-terminal 20-amino acid segment of SEQ ID NO: 2 or delete or substitute the cysteine residues at positions 7 and 10 of SEQ ID NO: 2. Even when cysteine residues are removed, the single chain Fc domains can still form a dimeric Fc domain that is held together non-covalently.
- 15 2. A native Fc is modified to make it more compatible with a selected host cell. For example, one may remove the PA sequence near the N-terminus of a typical native Fc, which may be recognized by a digestive enzyme in E. coli such as proline iminopeptidase. One may also add an N-terminal methionine residue, especially when the molecule is
20 expressed recombinantly in a bacterial cell such as E. coli. The Fc domain of SEQ ID NO: 2 is one such Fc variant.
3. A portion of the N-terminus of a native Fc is removed to prevent N-terminal heterogeneity when expressed in a selected host cell. For this purpose, one may delete any of the first 20 amino acid residues at the
25 N-terminus, particularly those at positions 1, 2, 3, 4 and 5.
4. One or more glycosylation sites are removed. Residues that are typically glycosylated (e.g., asparagine) may confer cytolytic response. Such residues may be deleted or substituted with unglycosylated residues (e.g., alanine).

5. Sites involved in interaction with complement, such as the C1q binding site, are removed. For example, one may delete or substitute the EKK sequence of human IgG1. Complement recruitment may not be advantageous for the molecules of this invention and so may be avoided with such an Fc variant.
6. Sites are removed that affect binding to Fc receptors other than a salvage receptor. A native Fc may have sites for interaction with certain white blood cells that are not required for the fusion molecules of the present invention and so may be removed.
7. The ADCC site is removed. ADCC sites are known in the art; see, for example, Molec. Immunol. 29 (5): 633-9 (1992) with regard to ADCC sites in IgG1. These sites, as well, are not required for the fusion molecules of the present invention and so may be removed.
8. When the native Fc is derived from a non-human antibody, the native Fc may be humanized. Typically, to humanize a native Fc, one will substitute selected residues in the non-human native Fc with residues that are normally found in human native Fc. Techniques for antibody humanization are well known in the art.

Preferred Fc variants include the following. In SEQ ID NO: 2 (Figure 3), the leucine at position 15 may be substituted with glutamate; the glutamate at position 99, with alanine; and the lysines at positions 101 and 103, with alanines. In addition, one or more tyrosine residues can be replaced by phenylalanine residues.

An alternative vehicle would be a protein, polypeptide, peptide, antibody, antibody fragment, or small molecule (e.g., a peptidomimetic compound) capable of binding to a salvage receptor. For example, one could use as a vehicle a polypeptide as described in U.S. Pat. No. 5,739,277, issued April 14, 1998 to Presta *et al.* Peptides could also be selected by phage display or RNA-peptide screening for binding to the

FcRn salvage receptor. Such salvage receptor-binding compounds are also included within the meaning of "vehicle" and are within the scope of this invention. Such vehicles should be selected for increased half-life (e.g., by avoiding sequences recognized by proteases) and decreased
5 immunogenicity (e.g., by favoring non-immunogenic sequences, as discovered in antibody humanization).

As noted above, polymer vehicles may also be used for V¹. Various means for attaching chemical moieties useful as vehicles are currently available, see, e.g., Patent Cooperation Treaty ("PCT") International
10 Publication No. WO 96/11953, entitled "N-Terminally Chemically Modified Protein Compositions and Methods," herein incorporated by reference in its entirety. This PCT publication discloses, among other things, the selective attachment of water soluble polymers to the N-terminus of proteins.

15 A preferred polymer vehicle is polyethylene glycol (PEG). The PEG group may be of any convenient molecular weight and may be linear or branched. The average molecular weight of the PEG will preferably range from about 2 kiloDalton ("kD") to about 100 kD, more preferably from about 5 kD to about 50 kD, most preferably from about 5 kD to about 10
20 kD. The PEG groups will generally be attached to the compounds of the invention via acylation or reductive alkylation through a reactive group on the PEG moiety (e.g., an aldehyde, amino, thiol, or ester group) to a reactive group on the inventive compound (e.g., an aldehyde, amino, or ester group).

25 A useful strategy for the PEGylation of synthetic peptides consists of combining, through forming a conjugate linkage in solution, a peptide and a PEG moiety, each bearing a special functionality that is mutually reactive toward the other. The peptides can be easily prepared with conventional solid phase synthesis. The peptides are "preactivated" with

an appropriate functional group at a specific site. The precursors are purified and fully characterized prior to reacting with the PEG moiety. Ligation of the peptide with PEG usually takes place in aqueous phase and can be easily monitored by reverse phase analytical HPLC. The PEGylated peptides can be easily purified by preparative HPLC and characterized by analytical HPLC, amino acid analysis and laser desorption mass spectrometry.

Polysaccharide polymers are another type of water soluble polymer which may be used for protein modification. Dextran is polysaccharide polymers comprised of individual subunits of glucose predominantly linked by α 1-6 linkages. The dextran itself is available in many molecular weight ranges, and is readily available in molecular weights from about 1 kD to about 70 kD. Dextran is a suitable water soluble polymer for use in the present invention as a vehicle by itself or in combination with another vehicle (e.g., Fc). See, for example, WO 96/11953 and WO 96/05309. The use of dextran conjugated to therapeutic or diagnostic immunoglobulins has been reported; see, for example, European Patent Publication No. 0 315 456, which is hereby incorporated by reference in its entirety. Dextran of about 1 kD to about 20 kD is preferred when dextran is used as a vehicle in accordance with the present invention.

Linkers. Any "linker" group is optional. When present, its chemical structure is not critical, since it serves primarily as a spacer. The linker is preferably made up of amino acids linked together by peptide bonds. Thus, in preferred embodiments, the linker is made up of from 1 to 30 amino acids linked by peptide bonds, wherein the amino acids are selected from the 20 naturally occurring amino acids. Some of these amino acids may be glycosylated, as is well understood by those in the art. In a more preferred embodiment, the 1 to 20 amino acids are selected from glycine, alanine, proline, asparagine, glutamine, and lysine. Even more preferably,

a linker is made up of a majority of amino acids that are sterically unhindered, such as glycine and alanine. Thus, preferred linkers are polyglycines (particularly (Gly)₄, (Gly)₅), poly(Gly-Ala), and polyalanines. Other specific examples of linkers are:

- 5 (Gly)₃Lys(Gly)₄ (SEQ ID NO: 40);
 (Gly)₃AsnGlySer(Gly)₂ (SEQ ID NO: 41);
 (Gly)₃Cys(Gly)₄ (SEQ ID NO: 42); and
 GlyProAsnGlyGly (SEQ ID NO: 43).

To explain the above nomenclature, for example, (Gly)₃Lys(Gly)₄ means
 10 Gly-Gly-Gly-Lys-Gly-Gly-Gly-Gly (SEQ ID NO: 40). Combinations of Gly and Ala are also preferred. The linkers shown here are exemplary; linkers within the scope of this invention may be much longer and may include other residues.

Preferred linkers are amino acid linkers comprising greater than 5
 15 amino acids, with suitable linkers having up to about 500 amino acids selected from glycine, alanine, proline, asparagine, glutamine, lysine, threonine, serine or aspartate. Linkers of about 20 to 50 amino acids are most preferred. One group of preferred linkers are those of the formulae

20 GSGSATGGSGSTASSGSGSATx¹x²
 (SEQ ID NO: 193)

and

GSGSATGGSGSTASSGSGSATx¹x²GSGSATGGSGSTASSGSGSATx³x⁴
 (SEQ ID NO: 194)

wherein x¹ and x³ are each independently basic or hydrophobic residues
 25 and x² and x⁴ are each independently hydrophobic residues. Specific preferred linkers are:

GSGSATGGSGSTASSGSGSATHM
 (SEQ ID NO: 59)

GSGSATGGSGSTASSGSGSATGM

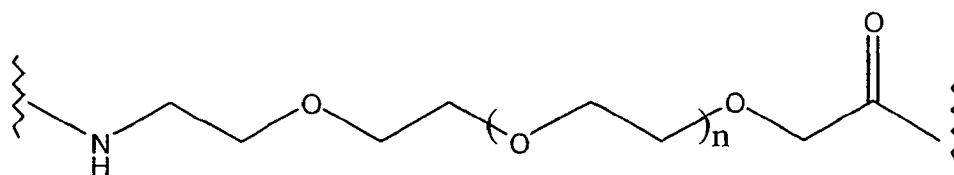
(SEQ ID NO: 190)

GSGSATGGSGSTASSGSGSATGS

(SEQ ID NO: 191), and

5 GSGSATGGSGSTASSGSGSATHMGSATGGSGSTASSGSGSATHM
(SEQ ID NO: 192).

Non-peptide linkers are also possible. For example, alkyl linkers such as $-\text{NH}-(\text{CH}_2)_s-\text{C}(\text{O})-$, wherein $s = 2-20$ could be used. These alkyl linkers may further be substituted by any non-sterically hindering group
10 such as lower alkyl (e.g., C_1-C_6) lower acyl, halogen (e.g., Cl, Br), CN, NH_2 , phenyl, etc. An exemplary non-peptide linker is a PEG linker,
VII



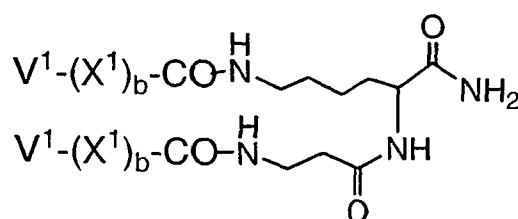
15 wherein n is such that the linker has a molecular weight of 100 to 5000 kD, preferably 100 to 500 kD. The peptide linkers may be altered to form derivatives in the same manner as described above.

Derivatives. The inventors also contemplate derivatizing the peptide and/or vehicle portion of the compounds. Such derivatives may
20 improve the solubility, absorption, biological half life, and the like of the compounds. The moieties may alternatively eliminate or attenuate any undesirable side-effect of the compounds and the like. Exemplary derivatives include compounds in which:

1. The compound or some portion thereof is cyclic. For example, the
25 peptide portion may be modified to contain two or more Cys residues (e.g., in the linker), which could cyclize by disulfide bond formation.

2. The compound is cross-linked or is rendered capable of cross-linking between molecules. For example, the peptide portion may be modified to contain one Cys residue and thereby be able to form an intermolecular disulfide bond with a like molecule. The compound may also be cross-linked through its C-terminus, as in the molecule shown below.

VIII



In Formula VIII, each "V¹" may represent typically one strand of the Fc domain.

3. One or more peptidyl [-C(O)NR-] linkages (bonds) is replaced by a non-peptidyl linkage. Exemplary non-peptidyl linkages are -CH₂-carbamate [-CH₂-OC(O)NR-], phosphonate, -CH₂-sulfonamide [-CH₂-S(O)₂NR-], urea [-NHC(O)NH-], -CH₂-secondary amine, and alkylated peptide [-C(O)NR⁶- wherein R⁶ is lower alkyl].
4. The N-terminus is derivatized. Typically, the N-terminus may be acylated or modified to a substituted amine. Exemplary N-terminal derivative groups include -NRR¹ (other than -NH₂), -NRC(O)R¹, -NRC(O)OR¹, -NRS(O)₂R¹, -NHC(O)NHR¹, succinimide, or benzyloxycarbonyl-NH- (CBZ-NH-), wherein R and R¹ are each independently hydrogen or lower alkyl and wherein the phenyl ring may be substituted with 1 to 3 substituents selected from the group consisting of C₁-C₄ alkyl, C₁-C₄ alkoxy, chloro, and bromo.
5. The free C-terminus is derivatized. Typically, the C-terminus is esterified or amidated. Exemplary C-terminal derivative groups include, for example, -C(O)R² wherein R² is lower alkoxy or -NR³R⁴

wherein R³ and R⁴ are independently hydrogen or C₁-C₈ alkyl (preferably C₁-C₄ alkyl).

6. A disulfide bond is replaced with another, preferably more stable, cross-linking moiety (e.g., an alkylene). See, e.g., Bhatnagar *et al.* (1996), *J. Med. Chem.* 39: 3814-9; Alberts *et al.* (1993) *Thirteenth Am. Pep. Symp.*, 357-9.
7. One or more individual amino acid residues is modified. Various derivatizing agents are known to react specifically with selected sidechains or terminal residues, as described in detail below.

10 Lysinyl residues and amino terminal residues may be reacted with succinic or other carboxylic acid anhydrides, which reverse the charge of the lysinyl residues. Other suitable reagents for derivatizing alpha-amino-containing residues include imidoesters such as methyl picolinimate; pyridoxal phosphate; pyridoxal; chloroborohydride; trinitrobenzenesulfonic
15 acid; O-methylisourea; 2,4 pentanedione; and transaminase-catalyzed reaction with glyoxylate.

Arginyl residues may be modified by reaction with any one or combination of several conventional reagents, including phenylglyoxal, 2,3-butanedione, 1,2-cyclohexanedione, and ninhydrin. Derivatization of arginyl
20 residues requires that the reaction be performed in alkaline conditions because of the high pKa of the guanidine functional group. Furthermore, these reagents may react with the groups of lysine as well as the arginine epsilon-amino group.

Specific modification of tyrosyl residues has been studied extensively,
25 with particular interest in introducing spectral labels into tyrosyl residues by reaction with aromatic diazonium compounds or tetranitromethane. Most commonly, N-acetylimidazole and tetranitromethane are used to form O-acetyl tyrosyl species and 3-nitro derivatives, respectively.

Carboxyl sidechain groups (aspartyl or glutamyl) may be selectively modified by reaction with carbodiimides ($R'-N=C=N-R'$) such as 1-cyclohexyl-3-(2-morpholinyl-(4-ethyl) carbodiimide or 1-ethyl-3-(4-azonia-4,4-dimethylpentyl) carbodiimide. Furthermore, aspartyl and glutamyl residues
5 may be converted to asparaginyl and glutaminyl residues by reaction with ammonium ions.

Glutaminyl and asparaginyl residues may be deamidated to the corresponding glutamyl and aspartyl residues. Alternatively, these residues are deamidated under mildly acidic conditions. Either form of these residues
10 falls within the scope of this invention.

Cysteinyl residues can be replaced by amino acid residues or other moieties either to eliminate disulfide bonding or, conversely, to stabilize cross-linking. See, e.g., Bhatnagar *et al.* (1996), *J. Med. Chem.* 39: 3814-9.

Derivatization with bifunctional agents is useful for cross-linking the
15 peptides or their functional derivatives to a water-insoluble support matrix or to other macromolecular vehicles. Commonly used cross-linking agents include, e.g., 1,1-bis(diazoacetyl)-2-phenylethane, glutaraldehyde, N-hydroxysuccinimide esters, for example, esters with 4-azidosalicylic acid, homobifunctional imidoesters, including disuccinimidyl esters such as 3,3'-
20 dithiobis(succinimidylpropionate), and bifunctional maleimides such as bis-N-maleimido-1,8-octane. Derivatizing agents such as methyl-3-[(p-azidophenyl)dithio]propioimide yield photoactivatable intermediates that are capable of forming cross-links in the presence of light. Alternatively, reactive water-insoluble matrices such as cyanogen bromide-activated carbohydrates
25 and the reactive substrates described in U.S. Pat. Nos. 3,969,287; 3,691,016; 4,195,128; 4,247,642; 4,229,537; and 4,330,440 are employed for protein immobilization.

Carbohydrate (oligosaccharide) groups may conveniently be attached to sites that are known to be glycosylation sites in proteins.

Generally, O-linked oligosaccharides are attached to serine (Ser) or threonine (Thr) residues while N-linked oligosaccharides are attached to asparagine (Asn) residues when they are part of the sequence Asn-X-Ser/Thr, where X can be any amino acid except proline. X is preferably
5 one of the 19 naturally occurring amino acids other than proline. The structures of N-linked and O-linked oligosaccharides and the sugar residues found in each type are different. One type of sugar that is commonly found on both is N-acetylneuraminic acid (referred to as sialic acid). Sialic acid is usually the terminal residue of both N-linked and O-
10 linked oligosaccharides and, by virtue of its negative charge, may confer acidic properties to the glycosylated compound. Such site(s) may be incorporated in the linker of the compounds of this invention and are preferably glycosylated by a cell during recombinant production of the polypeptide compounds (e.g., in mammalian cells such as CHO, BHK,
15 COS). However, such sites may further be glycosylated by synthetic or semi-synthetic procedures known in the art.

Other possible modifications include hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, oxidation of the sulfur atom in Cys, methylation of the alpha-amino
20 groups of lysine, arginine, and histidine side chains. Creighton, Proteins: Structure and Molecule Properties (W. H. Freeman & Co., San Francisco), pp. 79-86 (1983).

Compounds of the present invention may be changed at the DNA level, as well. The DNA sequence of any portion of the compound may be
25 changed to codons more compatible with the chosen host cell. For E. coli, which is the preferred host cell, optimized codons are known in the art. Codons may be substituted to eliminate restriction sites or to include silent restriction sites, which may aid in processing of the DNA in the selected

host cell. The vehicle, linker and peptide DNA sequences may be modified to include any of the foregoing sequence changes.

Methods of Making

The compounds of this invention largely may be made in
5 transformed host cells using recombinant DNA techniques. To do so, a recombinant DNA molecule coding for the peptide is prepared. Methods of preparing such DNA molecules are well known in the art. For instance, sequences coding for the peptides could be excised from DNA using suitable restriction enzymes. Alternatively, the DNA molecule could be
10 synthesized using chemical synthesis techniques, such as the phosphoramidate method. Also, a combination of these techniques could be used.

The invention also includes a vector capable of expressing the peptides in an appropriate host. The vector comprises the DNA molecule
15 that codes for the peptides operatively linked to appropriate expression control sequences. Methods of effecting this operative linking, either before or after the DNA molecule is inserted into the vector, are well known. Expression control sequences include promoters, activators, enhancers, operators, ribosomal binding sites, start signals, stop signals,
20 cap signals, polyadenylation signals, and other signals involved with the control of transcription or translation.

The resulting vector having the DNA molecule thereon is used to transform an appropriate host. This transformation may be performed using methods well known in the art.

25 Any of a large number of available and well-known host cells may be used in the practice of this invention. The selection of a particular host is dependent upon a number of factors recognized by the art. These include, for example, compatibility with the chosen expression vector, toxicity of the peptides encoded by the DNA molecule, rate of

transformation, ease of recovery of the peptides, expression characteristics, bio-safety and costs. A balance of these factors must be struck with the understanding that not all hosts may be equally effective for the expression of a particular DNA sequence. Within these general guidelines, 5 useful microbial hosts include bacteria (such as E. coli sp.), yeast (such as Saccharomyces sp.) and other fungi, insects, plants, mammalian (including human) cells in culture, or other hosts known in the art.

Next, the transformed host is cultured and purified. Host cells may be cultured under conventional fermentation conditions so that the 10 desired compounds are expressed. Such fermentation conditions are well known in the art. Finally, the peptides are purified from culture by methods well known in the art.

The compounds may also be made by synthetic methods. For example, solid phase synthesis techniques may be used. Suitable 15 techniques are well known in the art, and include those described in Merrifield (1973), Chem. Polypeptides, pp. 335-61 (Katsoyannis and Panayotis eds.); Merrifield (1963), J. Am. Chem. Soc. 85: 2149; Davis et al. (1985), Biochem. Intl. 10: 394-414; Stewart and Young (1969), Solid Phase Peptide Synthesis; U.S. Pat. No. 3,941,763; Finn et al. (1976), The Proteins 20 (3rd ed.) 2: 105-253; and Erickson et al. (1976), The Proteins (3rd ed.) 2: 257-527. Solid phase synthesis is the preferred technique of making individual peptides since it is the most cost-effective method of making small peptides.

Compounds that contain derivatized peptides or which contain 25 non-peptide groups may be synthesized by well-known organic chemistry techniques.

Uses of the Compounds

Compounds of this invention may be particularly useful in treatment of B-cell mediated autoimmune diseases. In particular, the

compounds of this invention may be useful in treating, preventing, ameliorating, diagnosing or prognosing lupus, including systemic lupus erythematosus (SLE), and lupus-associated diseases and conditions. Other preferred indications include B-cell mediated cancers, including B-cell lymphoma.

The compounds of this invention can also be used to treat inflammatory conditions of the joints. Inflammatory conditions of a joint are chronic joint diseases that afflict and disable, to varying degrees, millions of people worldwide. Rheumatoid arthritis is a disease of articular joints in which the cartilage and bone are slowly eroded away by a proliferative, invasive connective tissue called pannus, which is derived from the synovial membrane. The disease may involve peri-articular structures such as bursae, tendon sheaths and tendons as well as extra-articular tissues such as the subcutis, cardiovascular system, lungs, spleen, lymph nodes, skeletal muscles, nervous system (central and peripheral) and eyes (Silberberg (1985), Anderson's Pathology, Kissane (ed.), II:1828). Osteoarthritis is a common joint disease characterized by degenerative changes in articular cartilage and reactive proliferation of bone and cartilage around the joint. Osteoarthritis is a cell-mediated active process that may result from the inappropriate response of chondrocytes to catabolic and anabolic stimuli. Changes in some matrix molecules of articular cartilage reportedly occur in early osteoarthritis (Thonar *et al.* (1993), Rheumatic disease clinics of North America, Moskowitz (ed.), 19:635-657 and Shinmei *et al.* (1992), *Arthritis Rheum.*, 35:1304-1308). TALL-1, TALL-1R and modulators thereof are believed to be useful in the treatment of these and related conditions.

Compounds of this invention may also be useful in treatment of a number of additional diseases and disorders, including:

- acute pancreatitis;

- ALS;
- Alzheimer's disease;
- asthma;
- atherosclerosis;
- 5 • autoimmune hemolytic anemia;
- cancer, particularly cancers related to B cells;
- cachexia/anorexia;
- chronic fatigue syndrome;
- cirrhosis (e.g., primary biliary cirrhosis);
- 10 • diabetes (e.g., insulin diabetes);
- fever;
- glomerulonephritis, including IgA glomerulonephritis and
primary glomerulonephritis;
- Goodpasture's syndrome;
- 15 • Guillain-Barre syndrome;
- graft versus host disease;
- Hashimoto's thyroiditis;
- hemorrhagic shock;
- hyperalgesia;
- 20 • inflammatory bowel disease;
- inflammatory conditions of a joint, including osteoarthritis,
psoriatic arthritis and rheumatoid arthritis;
- inflammatory conditions resulting from strain, sprain, cartilage
damage, trauma, orthopedic surgery, infection or other disease
25 processes;
- insulin-dependent diabetes mellitus;

- ischemic injury, including cerebral ischemia (e.g., brain injury as a result of trauma, epilepsy, hemorrhage or stroke, each of which may lead to neurodegeneration);
- learning impairment;
- 5 • lung diseases (e.g., ARDS);
- multiple myeloma;
- multiple sclerosis;
- Myasthenia gravis;
- myelogenous (e.g., AML and CML) and other leukemias;
- 10 • myopathies (e.g., muscle protein metabolism, esp. in sepsis);
- neurotoxicity (e.g., as induced by HIV);
- osteoporosis;
- pain;
- Parkinson's disease;
- 15 • Pemphigus;
- polymyositis/dermatomyositis;
- pulmonary inflammation, including autoimmune pulmonary inflammation;
- pre-term labor;
- 20 • psoriasis;
- Reiter's disease;
- reperfusion injury;
- septic shock;
- side effects from radiation therapy;
- 25 • Sjogren's syndrome;
- sleep disturbance;
- temporal mandibular joint disease;

- thrombocytopenia, including idiopathic thrombocytopenia and autoimmune neonatal thrombocytopenia;
- tumor metastasis;
- uveitis; and
- 5 • vasculitis.

Compounds of this invention may be administered alone or in combination with a therapeutically effective amount of other drugs, including analgesic agents, disease-modifying anti-rheumatic drugs (DMARDs), non-steroidal anti-inflammatory drugs (NSAIDs), and any
10 immune and/or inflammatory modulators. Thus, compounds of this invention may be administered with:

- Modulators of other members of the TNF/TNF receptor family, including TNF antagonists, such as etanercept (Enbrel™), sTNF-RI, onercept, D2E7, and Remicade™.
- 15 • Nerve growth factor (NGF) modulators.
- IL-1 inhibitors, including IL-1ra molecules such as anakinra and more recently discovered IL-1ra-like molecules such as IL-1Hy1 and IL-1Hy2; IL-1 "trap" molecules as described in U.S. Pat. No. 5,844,099, issued December 1, 1998; IL-1 antibodies; solubilized
20 IL-1 receptor, and the like.
- IL-6 inhibitors (e.g., antibodies to IL-6).
- IL-8 inhibitors (e.g., antibodies to IL-8).
- IL-18 inhibitors (e.g., IL-18 binding protein, solubilized IL-18 receptor, or IL-18 antibodies).
- 25 • Interleukin-1 converting enzyme (ICE) modulators.
- insulin-like growth factors (IGF-1, IGF-2) and modulators thereof.
- Transforming growth factor- β (TGF- β), TGF- β family members, and TGF- β modulators.

- Fibroblast growth factors FGF-1 to FGF-10, and FGF modulators.
- Osteoprotegerin (OPG), OPG analogues, osteoprotective agents, and antibodies to OPG-ligand (OPG-L).
- 5 • bone anabolic agents, such as parathyroid hormone (PTH), PTH fragments, and molecules incorporating PTH fragments (e.g., PTH (1-34)-Fc).
- PAF antagonists.
- Keratinocyte growth factor (KGF), KGF-related molecules (e.g.,
10 KGF-2), and KGF modulators.
- COX-2 inhibitors, such as Celebrex™ and Vioxx™.
- Prostaglandin analogs (e.g., E series prostaglandins).
- Matrix metalloproteinase (MMP) modulators.
- Nitric oxide synthase (NOS) modulators, including modulators
15 of inducible NOS.
- Modulators of glucocorticoid receptor.
- Modulators of glutamate receptor.
- Modulators of lipopolysaccharide (LPS) levels.
- Anti-cancer agents, including inhibitors of oncogenes (e.g., fos,
20 jun) and interferons.
- Noradrenaline and modulators and mimetics thereof.

Pharmaceutical Compositions

In General. The present invention also provides methods of using pharmaceutical compositions of the inventive compounds. Such pharmaceutical compositions may be for administration for injection, or for
5 oral, pulmonary, nasal, transdermal or other forms of administration. In general, the invention encompasses pharmaceutical compositions comprising effective amounts of a compound of the invention together with pharmaceutically acceptable diluents, preservatives, solubilizers, emulsifiers, adjuvants and/or carriers. Such compositions include diluents of various
10 buffer content (e.g., Tris-HCl, acetate, phosphate), pH and ionic strength; additives such as detergents and solubilizing agents (e.g., Tween 80, Polysorbate 80), anti-oxidants (e.g., ascorbic acid, sodium metabisulfite), preservatives (e.g., Thimersol, benzyl alcohol) and bulking substances (e.g., lactose, mannitol); incorporation of the material into particulate preparations of
15 polymeric compounds such as polylactic acid, polyglycolic acid, etc. or into liposomes. Hyaluronic acid may also be used, and this may have the effect of promoting sustained duration in the circulation. Such compositions may influence the physical state, stability, rate of in vivo release, and rate of in vivo clearance of the present proteins and derivatives. See, e.g., Remington's
20 Pharmaceutical Sciences, 18th Ed. (1990, Mack Publishing Co., Easton, PA 18042) pages 1435-1712 which are herein incorporated by reference in their entirety. The compositions may be prepared in liquid form, or may be in dried powder, such as lyophilized form. Implantable sustained release formulations are also contemplated, as are transdermal formulations.

25 Oral dosage forms. Contemplated for use herein are oral solid dosage forms, which are described generally in Chapter 89 of Remington's Pharmaceutical Sciences (1990), 18th Ed., Mack Publishing Co. Easton PA 18042, which is herein incorporated by reference in its entirety. Solid dosage forms include tablets, capsules, pills, troches or lozenges, cachets

or pellets. Also, liposomal or proteinoid encapsulation may be used to formulate the present compositions (as, for example, proteinoid microspheres reported in U.S. Patent No. 4,925,673). Liposomal encapsulation may be used and the liposomes may be derivatized with various polymers (e.g., U.S. Patent No. 5,013,556). A description of possible solid dosage forms for the therapeutic is given in Chapter 10 of Marshall, K., Modern Pharmaceutics (1979), edited by G. S. Banker and C. T. Rhodes, herein incorporated by reference in its entirety. In general, the formulation will include the inventive compound, and inert ingredients which allow for protection against the stomach environment, and release of the biologically active material in the intestine.

Also specifically contemplated are oral dosage forms of the above inventive compounds. If necessary, the compounds may be chemically modified so that oral delivery is efficacious. Generally, the chemical modification contemplated is the attachment of at least one moiety to the compound molecule itself, where said moiety permits (a) inhibition of proteolysis; and (b) uptake into the blood stream from the stomach or intestine. Also desired is the increase in overall stability of the compound and increase in circulation time in the body. Moieties useful as covalently attached vehicles in this invention may also be used for this purpose. Examples of such moieties include: PEG, copolymers of ethylene glycol and propylene glycol, carboxymethyl cellulose, dextran, polyvinyl alcohol, polyvinyl pyrrolidone and polyproline. See, for example, Abuchowski and Davis, Soluble Polymer-Enzyme Adducts, Enzymes as Drugs (1981), Hocenberg and Roberts, eds., Wiley-Interscience, New York, NY, , pp. 367-83; Newmark, et al. (1982), J. Appl. Biochem. 4:185-9. Other polymers that could be used are poly-1,3-dioxolane and poly-1,3,6-tioxocane. Preferred for pharmaceutical usage, as indicated above, are PEG moieties.

For oral delivery dosage forms, it is also possible to use a salt of a modified aliphatic amino acid, such as sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC), as a carrier to enhance absorption of the therapeutic compounds of this invention. The clinical efficacy of a heparin
5 formulation using SNAC has been demonstrated in a Phase II trial conducted by Emisphere Technologies. See US Patent No. 5,792,451, "Oral drug delivery composition and methods".

The compounds of this invention can be included in the formulation as fine multiparticulates in the form of granules or pellets of
10 particle size about 1 mm. The formulation of the material for capsule administration could also be as a powder, lightly compressed plugs or even as tablets. The therapeutic could be prepared by compression.

Colorants and flavoring agents may all be included. For example, the protein (or derivative) may be formulated (such as by liposome or
15 microsphere encapsulation) and then further contained within an edible product, such as a refrigerated beverage containing colorants and flavoring agents.

One may dilute or increase the volume of the compound of the invention with an inert material. These diluents could include
20 carbohydrates, especially mannitol, α -lactose, anhydrous lactose, cellulose, sucrose, modified dextrans and starch. Certain inorganic salts may also be used as fillers including calcium triphosphate, magnesium carbonate and sodium chloride. Some commercially available diluents are Fast-Flo, Emdex, STA-Rx 1500, Emcompress and Avicell.

25 Disintegrants may be included in the formulation of the therapeutic into a solid dosage form. Materials used as disintegrants include but are not limited to starch including the commercial disintegrant based on starch, Explotab. Sodium starch glycolate, Amberlite, sodium carboxymethylcellulose, ultramylopectin, sodium alginate, gelatin, orange

peel, acid carboxymethyl cellulose, natural sponge and bentonite may all be used. Another form of the disintegrants are the insoluble cationic exchange resins. Powdered gums may be used as disintegrants and as binders and these can include powdered gums such as agar, Karaya or tragacanth. Alginic acid and its sodium salt are also useful as
5 disintegrants.

Binders may be used to hold the therapeutic agent together to form a hard tablet and include materials from natural products such as acacia, tragacanth, starch and gelatin. Others include methyl cellulose (MC), ethyl
10 cellulose (EC) and carboxymethyl cellulose (CMC). Polyvinyl pyrrolidone (PVP) and hydroxypropylmethyl cellulose (HPMC) could both be used in alcoholic solutions to granulate the therapeutic.

An antifrictional agent may be included in the formulation of the therapeutic to prevent sticking during the formulation process. Lubricants
15 may be used as a layer between the therapeutic and the die wall, and these can include but are not limited to; stearic acid including its magnesium and calcium salts, polytetrafluoroethylene (PTFE), liquid paraffin, vegetable oils and waxes. Soluble lubricants may also be used such as sodium lauryl sulfate, magnesium lauryl sulfate, polyethylene glycol of
20 various molecular weights, Carbowax 4000 and 6000.

Glidants that might improve the flow properties of the drug during formulation and to aid rearrangement during compression might be added. The glidants may include starch, talc, pyrogenic silica and hydrated silicoaluminate.

25 To aid dissolution of the compound of this invention into the aqueous environment a surfactant might be added as a wetting agent. Surfactants may include anionic detergents such as sodium lauryl sulfate, dioctyl sodium sulfosuccinate and dioctyl sodium sulfonate. Cationic detergents might be used and could include benzalkonium chloride or

benzethonium chloride. The list of potential nonionic detergents that could be included in the formulation as surfactants are lauromacrogol 400, polyoxyl 40 stearate, polyoxyethylene hydrogenated castor oil 10, 50 and 60, glycerol monostearate, polysorbate 40, 60, 65 and 80, sucrose fatty acid
5 ester, methyl cellulose and carboxymethyl cellulose. These surfactants could be present in the formulation of the protein or derivative either alone or as a mixture in different ratios.

Additives may also be included in the formulation to enhance uptake of the compound. Additives potentially having this property are
10 for instance the fatty acids oleic acid, linoleic acid and linolenic acid.

Controlled release formulation may be desirable. The compound of this invention could be incorporated into an inert matrix which permits release by either diffusion or leaching mechanisms; e.g., gums. Slowly degenerating matrices may also be incorporated into the formulation, e.g.,
15 alginates, polysaccharides. Another form of a controlled release of the compounds of this invention is by a method based on the Oros therapeutic system (Alza Corp.), i.e., the drug is enclosed in a semipermeable membrane which allows water to enter and push drug out through a single small opening due to osmotic effects. Some enteric coatings also
20 have a delayed release effect.

Other coatings may be used for the formulation. These include a variety of sugars which could be applied in a coating pan. The therapeutic agent could also be given in a film coated tablet and the materials used in this instance are divided into 2 groups. The first are the nonenteric
25 materials and include methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, methylhydroxy-ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl-methyl cellulose, sodium carboxy-methyl cellulose, providone and the polyethylene glycols. The second group consists of the enteric materials that are commonly esters of phthalic acid.

A mix of materials might be used to provide the optimum film coating. Film coating may be carried out in a pan coater or in a fluidized bed or by compression coating.

Pulmonary delivery forms. Also contemplated herein is pulmonary
5 delivery of the present protein (or derivatives thereof). The protein (or
derivative) is delivered to the lungs of a mammal while inhaling and
traverses across the lung epithelial lining to the blood stream. (Other
reports of this include Adjei *et al.*, Pharma. Res. (1990) 7: 565-9; Adjei *et al.*
(1990), Internatl. J. Pharmaceutics 63: 135-44 (leuprolide acetate); Braquet
10 *et al.* (1989), J. Cardiovasc. Pharmacol. 13 (suppl.5): s.143-146 (endothelin-
1); Hubbard *et al.* (1989), Annals Int. Med. 3: 206-12 (α 1-antitrypsin); Smith
et al. (1989), J. Clin. Invest. 84: 1145-6 (α 1-proteinase); Oswein *et al.* (March
1990), "Aerosolization of Proteins", Proc. Symp. Resp. Drug Delivery II,
Keystone, Colorado (recombinant human growth hormone); Debs *et al.*
15 (1988), J. Immunol. 140: 3482-8 (interferon- γ and tumor necrosis factor α)
and Platz *et al.*, U.S. Patent No. 5,284,656 (granulocyte colony stimulating
factor).

Contemplated for use in the practice of this invention are a wide
range of mechanical devices designed for pulmonary delivery of
20 therapeutic products, including but not limited to nebulizers, metered
dose inhalers, and powder inhalers, all of which are familiar to those
skilled in the art. Some specific examples of commercially available
devices suitable for the practice of this invention are the Ultravent
nebulizer, manufactured by Mallinckrodt, Inc., St. Louis, Missouri; the
25 Acorn II nebulizer, manufactured by Marquest Medical Products,
Englewood, Colorado; the Ventolin metered dose inhaler, manufactured
by Glaxo Inc., Research Triangle Park, North Carolina; and the Spinhaler
powder inhaler, manufactured by Fisons Corp., Bedford, Massachusetts.

All such devices require the use of formulations suitable for the dispensing of the inventive compound. Typically, each formulation is specific to the type of device employed and may involve the use of an appropriate propellant material, in addition to diluents, adjuvants
5 and/or carriers useful in therapy.

The inventive compound should most advantageously be prepared in particulate form with an average particle size of less than 10 μm (or microns), most preferably 0.5 to 5 μm , for most effective delivery to the distal lung.

10 Pharmaceutically acceptable carriers include carbohydrates such as trehalose, mannitol, xylitol, sucrose, lactose, and sorbitol. Other ingredients for use in formulations may include DPPC, DOPE, DSPC and DOPC. Natural or synthetic surfactants may be used. PEG may be used (even apart from its use in derivatizing the protein or analog).
15 Dextrans, such as cyclodextran, may be used. Bile salts and other related enhancers may be used. Cellulose and cellulose derivatives may be used. Amino acids may be used, such as use in a buffer formulation.

Also, the use of liposomes, microcapsules or microspheres, inclusion complexes, or other types of carriers is contemplated.

20 Formulations suitable for use with a nebulizer, either jet or ultrasonic, will typically comprise the inventive compound dissolved in water at a concentration of about 0.1 to 25 mg of biologically active protein per mL of solution. The formulation may also include a buffer and a simple sugar (e.g., for protein stabilization and regulation of osmotic
25 pressure). The nebulizer formulation may also contain a surfactant, to reduce or prevent surface induced aggregation of the protein caused by atomization of the solution in forming the aerosol.

Formulations for use with a metered-dose inhaler device will generally comprise a finely divided powder containing the inventive

compound suspended in a propellant with the aid of a surfactant. The propellant may be any conventional material employed for this purpose, such as a chlorofluorocarbon, a hydrochlorofluorocarbon, a hydrofluorocarbon, or a hydrocarbon, including trichlorofluoromethane, dichlorodifluoromethane, dichlorotetrafluoroethanol, and 1,1,1,2-
5 tetrafluoroethane, or combinations thereof. Suitable surfactants include sorbitan trioleate and soya lecithin. Oleic acid may also be useful as a surfactant.

Formulations for dispensing from a powder inhaler device will
10 comprise a finely divided dry powder containing the inventive compound and may also include a bulking agent, such as lactose, sorbitol, sucrose, mannitol, trehalose, or xylitol in amounts which facilitate dispersal of the powder from the device, e.g., 50 to 90% by weight of the formulation.

Nasal delivery forms. Nasal delivery of the inventive compound is
15 also contemplated. Nasal delivery allows the passage of the protein to the blood stream directly after administering the therapeutic product to the nose, without the necessity for deposition of the product in the lung. Formulations for nasal delivery include those with dextran or cyclodextran. Delivery via transport across other mucous membranes is
20 also contemplated.

Dosages. The dosage regimen involved in a method for treating the above-described conditions will be determined by the attending physician, considering various factors which modify the action of drugs, e.g. the age, condition, body weight, sex and diet of the patient, the severity of any infection,
25 time of administration and other clinical factors. Generally, the daily regimen should be in the range of 0.1-1000 micrograms of the inventive compound per kilogram of body weight, preferably 0.1-150 micrograms per kilogram.

Specific preferred embodiments

The inventors have determined preferred structures for the preferred peptides listed in Table 4 below. The symbol "Λ" may be any of the linkers described herein or may simply represent a normal peptide bond (i.e., so that no linker is present). Tandem repeats and linkers are shown separated by dashes for clarity.

Table 4—Preferred embodiments

Sequence/structure	SEQ ID NO:
LPGCKWDLLIKQWVCDPL-Λ-V ¹	44
V ¹ -Λ- LPGCKWDLLIKQWVCDPL	45
LPGCKWDLLIKQWVCDPL -Λ- LPGCKWDLLIKQWVCDPL -Λ-V ¹	46
V ¹ -Λ- LPGCKWDLLIKQWVCDPL -Λ- LPGCKWDLLIKQWVCDPL	47
SADCYFDILTKSDVCTSS-Λ-V ¹	48
V ¹ -Λ- SADCYFDILTKSDVCTSS	49
SADCYFDILTKSDVTSS-Λ- SADCYFDILTKSDVTSS -Λ-V ¹	50
V ¹ -Λ- SADCYFDILTKSDVTSS -Λ- SADCYFDILTKSDVTSS	51
FHDCKWDLLTKQWVCHGL-Λ-V ¹	52
V ¹ -Λ- FHDCKWDLLTKQWVCHGL	53
FHDCKWDLLTKQWVCHGL -Λ- FHDCKWDLLTKQWVCHGL -Λ-V ¹	54
V ¹ -Λ- FHDCKWDLLTKQWVCHGL -Λ- FHDCKWDLLTKQWVCHGL	55

"V¹" is an Fc domain as defined previously herein. In addition to those listed in Table 4, the inventors further contemplate heterodimers in which each strand of an Fc dimer is linked to a different peptide sequence; for example, wherein each Fc is linked to a different sequence selected from Table 2.

All of the compounds of this invention can be prepared by methods described in PCT appl. no. WO 99/25044.

The invention will now be further described by the following working examples, which are illustrative rather than limiting.

EXAMPLE 1

Peptides

5 Peptide Phage Display

1. Magnetic bead preparation

A. Fc-TALL-1 immobilization on magnetic beads

The recombinant Fc-TALL-1 protein was immobilized on the Protein A Dynabeads (Dyna) at a concentration of 8 μ g of Fc-TALL-1 per 100 μ l of the
10 bead stock from the manufacturer. By drawing the beads to one side of a tube using a magnet and pipetting away the liquid, the beads were washed twice with the phosphate buffer saline (PBS) and resuspended in PBS. The Fc-TALL-1 protein was added to the washed beads at the above concentration and incubated with rotation for 1 hour at room temperature. The Fc-TALL-1 coated beads were
15 then blocked by adding bovine serum albumin (BSA) to 1% final concentration and incubating overnight at 4 °C with rotation. The resulting Fc-TALL-1 coated beads were then washed twice with PBST (PBS with 0.05% Tween-20) before being subjected to the selection procedures.

B. Negative selection bead preparation

20 Additional beads were also prepared for negative selections. For each panning condition, 250 μ l of the bead stock from the manufacturer was subjected to the above procedure (section 1A) except that the incubation step with Fc-TALL-1 was omitted. In the last washing step, the beads were divided into five 50 μ l aliquots.

25 2. Selection of TALL-1 binding phage

A. Overall strategy

Two filamentous phage libraries, TN8-IX (5×10^9 independent transformants) and TN12-I (1.4×10^9 independent transformants) (Dyax Corp.), were used to select for TALL-1 binding phage. Each library was subjected to
30 either pH 2 elution or 'bead elution' (section 2E). Therefore, four different panning conditions were carried out for the TALL-1 project (TN8-IX using the

pH2 elution method, TN8-IX using the bead elution method, TN12-I the using pH2 elution method, and TN12-I using the bead elution method). Three rounds of selection were performed for each condition.

B. Negative selection

5 For each panning condition, about 100 random library equivalent (5×10^{11} pfu for TN8-IX and 1.4×10^{11} pfu for TN12-I) was aliquoted from the library stock and diluted to 300 μ l with PBST. After the last washing liquid was drawn out from the first 50 μ l aliquot of the beads prepared for negative selections (section 1B), the 300 μ l diluted library stock was added to the beads. The resulting
10 mixture was incubated for 10 minutes at room temperature with rotation. The phage supernatant was drawn out using the magnet and added to the second 50 μ l aliquot for another negative selection step. In this way, five negative selection steps were performed.

C. Selection using the Fc-TALL-1 protein coated beads

15 The phage supernatant after the last negative selection step (section 1B) was added to the Fc-TALL-1 coated beads after the last washing step (section 1A). This mixture was incubated with rotation for two hours at room temperature, allowing specific phage to bind to the target protein. After the supernatant is discarded, the beads were washed seven times with PBST.

20 D. pH2 elution of bound phage

After the last washing step (section 2C), the bound phages were eluted from the magnetic beads by adding 200 μ l of CBST (50 mM sodium citrate, 150 mM sodium chloride, 0.05% Tween-20, pH2). After 5 minute incubation at room temperature, the liquid containing the eluted phage were drawn out and transferred
25 to another tube. The elution step was repeated again by adding 200 μ l of CBST and incubating for 5 minutes. The liquids from two elution steps were added together, and 100 μ l of 2 M Tris solution (pH 8) was added to neutralize the pH. 500 μ l of Min A Salts solution (60 mM K_2HPO_4 , 33 mM KH_2PO_4 , 7.6 mM $(NH_4)SO_4$, and 1.7 mM sodium citrate) was added to make the final volume to 1
30 ml.

E. 'bead elution'

After the final washing liquid was drawn out (section 2C), 1 ml of Min A salts solution was added to the beads. This bead mixture was added directly to a concentrated bacteria sample for infection (section 3A and 3B).

5 3. Amplification

A. Preparation of plating cells

Fresh E. Coli. (XL-1 Blue MRF') culture was grown to $OD_{600} = 0.5$ in LB media containing 12.5 $\mu\text{g/ml}$ tetracycline. For each panning condition, 20 ml of this culture was chilled on ice and centrifuged. The bacteria pellet was
10 resuspended in 1 ml of the Min A Salts solution.

B. Transduction

Each mixture from different elution methods (section 2D and 2E) was added to a concentrated bacteria sample (section 3A) and incubated at 37 °C for 15 minutes. 2 ml of NZCYM media (2XNZCYM, 50 $\mu\text{g/ml}$ ampicillin) was
15 added to each mixture and incubated at room temperature for 15 minutes. The resulting 4 ml solution was plated on a large NZCYM agar plate containing 50 $\mu\text{g/ml}$ ampicillin and incubated overnight at 37 °C.

C. Phage Harvesting

Each of the bacteria/phage mixture that was grown overnight on a large
20 NZCYM agar plate (section 3B) was scraped off in 35 ml of LB media, and the agar plate was further rinsed with additional 35 ml of LB media. The resulting bacteria/phage mixture in LB media was centrifuged to pellet the bacteria away. 50 ml the of the phage supernatant was transferred to a fresh tube, and 12.5 ml of PEG solution (20% PEG8000, 3.5M ammonium acetate) was added and incubated
25 on ice for 2 hours to precipitate phages. Precipitated phages were centrifuged down and resuspended in 6 ml of the phage resuspension buffer (250 mM NaCl, 100 mM Tris pH8, 1 mM EDTA). This phage solution was further purified by centrifuging away the remaining bacteria and precipitating the phage for the second time by adding 1.5 ml of the PEG solution. After a centrifugation step, the
30 phage pellet was resuspended in 400 μl of PBS. This solution was subjected to a final centrifugation to rid of remaining bacteria debris. The resulting phage

preparation was titered by a standard plaque formation assay (Molecular Cloning, Maniatis et al 3rd Edition).

4. Two more rounds of selection and amplification.

In the second round, the amplified phage (10^{10} pfu) from the first round (section 3C) was used as the input phage to perform the selection and amplification steps (sections 2 and 3). The amplified phage (10^{10} pfu) from the 2nd round in turn was used as the input phage to perform 3rd round of selection and amplification (sections 2 and 3). After the elution steps (sections 2D and 2E) of the 3rd round, a small fraction of the eluted phage was plated out as in the plaque formation assay (section 3C). Individual plaques were picked and placed into 96 well microtiter plates containing 100 μ l of TE buffer in each well. These master plates were incubated in a 37 °C incubator for 1 hour to allow phages to elute into the TE buffer.

5. Clonal analysis (Phage ELISA and sequencing)

The phage clones were analyzed by phage ELISA and sequencing methods. The sequences were ranked based on the combined results from these two assays.

A. Phage ELISA

An XL-1 Blue MRF' culture was grown until OD₆₀₀ reaches 0.5. 30 μ l of this culture was aliquoted into each well of a 96 well microtiter plate. 10 μ l of eluted phage (section 4) was added to each well and allowed to infect bacteria for 15 min at room temperature. 130 μ l of LB media containing 12.5 μ g/ml of tetracycline and 50 μ g/ml of ampicillin was added to each well. The microtiter plate was then incubated overnight at 37 °C. The recombinant TALL-1 protein (1 μ g/ml in PBS) was allowed to coat onto the 96-well Maxisorp plates (NUNC) overnight and 4°C. As a control, the recombinant Fc-Trail protein was coated onto a separate Maxisorp plate at the same molar concentration as the TALL-1 protein.

On the following day, liquids in the protein coated Maxisorp plates were discarded, and each well was blocked with 300 μ l of 2% BSA solution at 37 °C

for one hour. The BSA solution was discarded, and the wells were washed three times with the PBST solution. After the last washing step, 50 μ l of PBST was added to each well of the protein coated Maxisorp plates. Each of the 50 μ l overnight cultures in the 96 well microtiter plate was transferred to the

5 corresponding wells of the TALL-1 coated plates as well as the control Fc-Trail coated plates. The 100 μ l mixtures in the two kinds of plates were incubated for 1 hour at room temperature. The liquid was discarded from the Maxisorp plates, and the wells were washed five times with PBST. The HRP-conjugated anti-M13 antibody (Pharmacia) was diluted to 1:7,500, and 100 μ l of the diluted solution

10 was added to each well of the Maxisorp plates for 1 hour incubation at room temperature. The liquid was again discarded and the wells were washed seven times with PBST. 100 μ l of tetramethylbenzidine (TMB) substrate (Sigma) was added to each well for the color reaction to develop, and the reaction was stopped with 50 μ l of the 5 N H₂SO₄ solution. The OD₄₅₀ was read on a plate

15 reader (Molecular Devices).

B. Sequencing of the phage clones.

For each phage clone, the sequencing template was prepared by a PCR method. The following oligonucleotide pair was used to amplify about 500 nucleotide fragment:

20 primer #1 (5'-CGGCGCAACTATCGGTATCAAGCTG-3') (SEQ ID NO: 56) and primer #2 (5'-CATGTACCGTAACACTGAGTTTCGTC-3'). (SEQ ID NO: 57)

The following mixture was prepared for each clone.

Reagents	volume (μ L) / tube
dH ₂ O	26.25
50% glycerol	10
10B PCR Buffer (w/o MgCl ₂)	5
25 mM MgCl ₂	4
10 mM dNTP mix	1
100 μ M primer 1	0.25
100 μ M primer 2	0.25
Taq polymerase	0.25
Phage in TE (section 4)	3
Final reaction volume	50

The thermocycler (GeneAmp PCR System 9700, Applied Biosystems) was used to run the following program: 94°C for 5 min; [94°C for 30 sec, 55°C for 30 sec, 72°C for 45 sec.]x30 cycles; 72°C for 7 min; cool to 4°C. The PCR product was checked by running 5 µl of each PCR reaction on a 1% agarose gel. The PCR product in the remaining 45 µl from each reaction was cleaned up using the QIAquick Multiwell PCR Purification kit (Qiagen), following the manufacturer's protocol. The resulting product was then sequenced using the ABI 377 Sequencer (Perkin-Elmer) following the manufacturer recommended protocol.

6. Sequence ranking and consensus sequence determination

A. Sequence ranking

The peptide sequences that were translated from variable nucleotide sequences (section 5B) were correlated to ELISA data. The clones that showed high OD₄₅₀ in the TALL-1 coated wells and low OD₄₅₀ in the Fc-Trail coated wells were considered more important. The sequences that occur multiple times were also considered important. Candidate sequences were chosen based on these criteria for further analysis as peptides or peptibodies. Five and nine candidate peptide sequences were selected from the TN8-IX and TN12-I libraries, respectively.

B. Consensus sequence determination

The majority of sequences selected from the TN12-I library contained a very conserved DBL motif. This motif was also observed in sequences selected from the TN8-IB library as well. Another motif, PFPWE (SEQ ID NO: 110) was also observed in sequences obtained from the TN8-IB library.

A consensus peptide, FHDCKWDLLTQWVCHGL (SEQ ID NO: 58), was designed based on the DBL motif. Since peptides derived from the TN12-I library were the most active ones, the top 26 peptide sequences based on the above ranking criteria (section 5A) were aligned by the DBL motif. The underlined "core amino acid sequence" was obtained by determining the amino acid that occur the most in each position. The two cysteines adjacent to the core

sequences were fixed amino acids in the TN12-I library. The rest of the amino acid sequence in the consensus peptide is taken from one of the candidate peptides, TALL-1-12-10 (Table 2, SEQ ID NO: 37). The peptide and peptibody that was derived from this consensus sequence were most active in the B cell proliferation assay.

EXAMPLE 2

Peptibodies

A set of 12 TALL-1 inhibitory peptibodies (Table 5) was constructed in which a monomer of each peptide was fused in-frame to the Fc region of human IgG1. Each TALL-1 inhibitory peptibody was constructed by annealing the pairs of oligonucleotides shown in Table 6 to generate a duplex encoding the peptide and a linker comprised of 5 glycine residues and one valine residue as an NdeI to SalI fragment. These duplex molecules were ligated into a vector (pAMG21-RANK-Fc, described herein) containing the human Fc gene, also digested with NdeI and SalI. The resulting ligation mixtures were transformed by electroporation into *E. coli* strain 2596 cells (GM221, described herein). Clones were screened for the ability to produce the recombinant protein product and to possess the gene fusion having the correct nucleotide sequence. A single such clone was selected for each of the peptibodies. The nucleotide and amino acid sequences of the fusion proteins are shown in Figure 4A through 4F.

Table 5. Peptide sequences and oligonucleotides used to generate TALL-1 inhibitory peptibodies.

Peptibody	Peptibody SEQ ID NO	Peptide Sequence	Sense oligo- nucleotide	Antisense oligo- nucleotide
TALL-1-8-1-a	29	PGTCFPPFWECTHA	2517-24	2517-25
TALL-1-8-2-a	30	WGACWPPFWECFKE	2517-26	2517-27
TALL-1-8-4-a	31	VPFCDLLTKHCFEA	2517-28	2517-29
TALL-1-12-4-a	32	GSRCKYKWDVLTQCFHH	2517-30	2517-31
TALL-1-12-3-a	33	LPGCKWDLLIKQWVCDPL	2517-32	2517-33
TALL-1-12-5-a	34	SADCYFDILTKSDVCTSS	2517-34	2517-35
TALL-1-12-8-a	35	SDDCMYDQLTRMFICSNL	2517-36	2517-37
TALL-1-12-9-a	36	DLNCKYDELTYKEWCQFN	2521-92	2521-93

TALL-1-12-10-a	37	FHDCKYDLLTRQMVCHGL	2521-94	2521-95
TALL-1-12-11-a	38	RNHCFWDHLLKQDPCSP	2521-96	2521-97
TALL-1-12-14-a	39	ANQCWWDLSLTKKNVCEFF	2521-98	2521-99
TALL-1-consensus	58	FHDCKWDLTLTKQWVCHGL	2551-48	2551-49

Table 5B TALL-1 inhibitory peptibodies.

Peptibody	Peptibody SEQ ID NO	Peptide Sequence			
TALL-1-8-1-a	111	MPGTCFFFPW VFLFPPKPKD DGVEVHNAKT KCKVSNKALP KNQVSLTCLV SDGSFFLYSK SLSLSPGK	ECTHAGGGGG TLMISRTPEV KPREEQYNST APIEKTISKA KGFYPSDIAV LTVDKSRWQQ	VDKTHTCPPC TCVVVDVSHE YRVVSVLTVL KGQPREPQVY EWESNGQPEN GNVFSCSVMH	PAPELLGGPS DPEVKFNWYV HQDWLNGKEY TLPPSRDELT NYKTTTPPVL EALHNHYTQK
TALL-1-8-2-a	112	MWGACWFPFW VFLFPPKPKD DGVEVHNAKT KCKVSNKALP KNQVSLTCLV SDGSFFLYSK SLSLSPGK	ECFKEGGGGG TLMISRTPEV KPREEQYNST APIEKTISKA KGFYPSDIAV LTVDKSRWQQ	VDKTHTCPPC TCVVVDVSHE YRVVSVLTVL KGQPREPQVY EWESNGQPEN GNVFSCSVMH	PAPELLGGPS DPEVKFNWYV HQDWLNGKEY TLPPSRDELT NYKTTTPPVL EALHNHYTQK
TALL-1-8-4-a	113	MVPFCDLLTK VFLFPPKPKD DGVEVHNAKT KCKVSNKALP KNQVSLTCLV SDGSFFLYSK SLSLSPGK	HCFEAGGGGG TLMISRTPEV KPREEQYNST APIEKTISKA KGFYPSDIAV LTVDKSRWQQ	VDKTHTCPPC TCVVVDVSHE YRVVSVLTVL KGQPREPQVY EWESNGQPEN GNVFSCSVMH	PAPELLGGPS DPEVKFNWYV HQDWLNGKEY TLPPSRDELT NYKTTTPPVL EALHNHYTQK
TALL-1-12-4-a	114	MGSRCYKWD GGPSVFLFPP NWYVDGVEVH GKEYKCKVSN DELTKNQVSL PVLDSGGSFF YTQKSLSLSP	VLTKQCFHHG KPKDTLMISR NAKTKPREEQ KALPAPIEKT TCLVKGFYPS LYSKLTVDKS GK	GGGGVDKTHT TPEVTCVVVD YNSTYRVVSV ISKAKGQPRE DIAVEWESNG RWQQGNVFSC	CPPCPAPELL VSHEDPEVKF LTVLHQDWLN PQVYTLPPSR QPENNYKTTP SVMHEALHNN
TALL-1-12-3-a	115	MLPGCKWDL GGPSVFLFPP NWYVDGVEVH GKEYKCKVSN DELTKNQVSL PVLDSGGSFF YTQKSLSLSP	IKQWVCDPLG KPKDTLMISR NAKTKPREEQ KALPAPIEKT TCLVKGFYPS LYSKLTVDKS GK	GGGGVDKTHT TPEVTCVVVD YNSTYRVVSV ISKAKGQPRE DIAVEWESNG RWQQGNVFSC	CPPCPAPELL VSHEDPEVKF LTVLHQDWLN PQVYTLPPSR QPENNYKTTP SVMHEALHNN
TALL-1-12-5-a	116	MSADCYFDIL GGPSVFLFPP NWYVDGVEVH GKEYKCKVSN DELTKNQVSL PVLDSGGSFF YTQKSLSLSP	TKSDVCTSSG KPKDTLMISR NAKTKPREEQ KALPAPIEKT TCLVKGFYPS LYSKLTVDKS GK	GGGG VDKTHT TPEVTCVVVD YNSTYRVVSV ISKAKGQPRE DIAVEWESNG RWQQGNVFSC	CPPCPAPELL VSHEDPEVKF LTVLHQDWLN PQVYTLPPSR QPENNYKTTP SVMHEALHNN
TALL-1-12-8-a	117	MSDDCMYDQL GGPSVFLFPP NWYVDGVEVH GKEYKCKVSN DELTKNQVSL	TRMFICSNLG KPKDTLMISR NAKTKPREEQ KALPAPIEKT TCLVKGFYPS	GGGGVDKTHT TPEVTCVVVD YNSTYRVVSV ISKAKGQPRE DIAVEWESNG	CPPCPAPELL VSHEDPEVKF LTVLHQDWLN PQVYTLPPSR QPENNYKTTP

		PVLDSGDSFF YTQKSLSLSP	LYSKLTVDKS GK	RWQQGNVFSC	SVMHEALHNNH
TALL-1-12-9-a	118	MDLNCKYDEL GGPSVFLFPP NWYVDGVEVH GKEYKCKVSN DELTKNQVSL PVLDSGDSFF YTQKSLSLSP	TYKEWCQFNG KPKDTLMISR NAKTKPREEQ KALPAPIEKT TCLVKGFYPS LYSKLTVDKS GK	GGGGVDKTHT TPEVTCVVVD YNSTYRVVSV ISKAKGQPRE DIAVEWESNG RWQQGNVFSC	CPPCPAPELL VSHEDPEVKF LTVLHQDWLN PQVYTLPPSR QPENNYKTP SVMHEALHNNH
TALL-1-12-10-a	119	MFHDCKYDLL GGPSVFLFPP NWYVDGVEVH GKEYKCKVSN DELTKNQVSL PVLDSGDSFF YTQKSLSLSP	TRQMVCHGLG KPKDTLMISR NAKTKPREEQ KALPAPIEKT TCLVKGFYPS LYSKLTVDKS GK	GGGGVDKTHT TPEVTCVVVD YNSTYRVVSV ISKAKGQPRE DIAVEWESNG RWQQGNVFSC	CPPCPAPELL VSHEDPEVKF LTVLHQDWLN PQVYTLPPSR QPENNYKTP SVMHEALHNNH
TALL-1-12-11-a	120	MRNHCFWDHL GGPSVFLFPP NWYVDGVEVH GKEYKCKVSN DELTKNQVSL PVLDSGDSFF YTQKSLSLSP	LKQDICPSPG KPKDTLMISR NAKTKPREEQ KALPAPIEKT TCLVKGFYPS LYSKLTVDKS GK	GGGGVDKTHT TPEVTCVVVD YNSTYRVVSV ISKAKGQPRE DIAVEWESNG RWQQGNVFSC	CPPCPAPELL VSHEDPEVKF LTVLHQDWLN PQVYTLPPSR QPENNYKTP SVMHEALHNNH
TALL-1-12-14-a	121	MANQCWWDLSL GGPSVFLFPP NWYVDGVEVH GKEYKCKVSN DELTKNQVSL PVLDSGDSFF YTQKSLSLSP	TKKNVCEFFG KPKDTLMISR NAKTKPREEQ KALPAPIEKT TCLVKGFYPS LYSKLTVDKS GK	GGGGVDKTHT TPEVTCVVVD YNSTYRVVSV ISKAKGQPRE DIAVEWESNG RWQQGNVFSC	CPPCPAPELL VSHEDPEVKF LTVLHQDWLN PQVYTLPPSR QPENNYKTP SVMHEALHNNH
TALL-1-consensus	122	MFHDCKWDL GGPSVFLFPP NWYVDGVEVH GKEYKCKVSN DELTKNQVSL PVLDSGDSFF YTQKSLSLSP	TKQWVCHGLG KPKDTLMISR NAKTKPREEQ KALPAPIEKT TCLVKGFYPS LYSKLTVDKS GK	GGGGVDKTHT TPEVTCVVVD YNSTYRVVSV ISKAKGQPRE DIAVEWESNG RWQQGNVFSC	CPPCPAPELL VSHEDPEVKF LTVLHQDWLN PQVYTLPPSR QPENNYKTP SVMHEALHNNH
TALL-1 12-3 tandem dimer	123	MLPGCKWDL HMLPGCKWDL LGGPSVFLFP FNWYVDGVEV NGKEYKCKVS RDELTKNQVS PPVLDSGDSF HYTQKSLSL	IKQWVCDPLG LIKQWVCDPL PKPKDTLMIS HNAKTKPREE NKALPAPIEK LTCLVKGFYP FLYSKLTVDK PGK	SGSATGGSGS GGGGGVDKTH RTPEVTCVVV QYNSTYRVVS TISKAKGQPR SDIAVEWESN SRWQQGNVFS	TASSGSGSAT TCPPCPAPEL DVSHEDPEVK VLTVLHQDWL EPQVYTLPPS GQPENNYKTT CSVMHEALHN
TALL-1 consensus tandem dimer	124	MFHDCKWDL HMFHDCKWDL LGGPSVFLFP FNWYVDGVEV NGKEYKCKVS RDELTKNQVS PPVLDSGDSF HYTQKSLSL	TKQWVCHGLG LTKQWVCHGL PKPKDTLMIS HNAKTKPREE NKALPAPIEK LTCLVKGFYP FLYSKLTVDK PGK	SGSATGGSGS GGGGGVDKTH RTPEVTCVVV QYNSTYRVVS TISKAKGQPR SDIAVEWESN SRWQQGNVFS	TASSGSGSAT DCPPCPAPEL DVSHEDPEVK VLTVLHQDWL EPQVYTLPPS GQPENNYKTT CSVMHEALHN

Table 6. Sequences of oligonucleotides used in peptibody construction.

Oligo-nucleotide ID number	SEQ ID NO	Sequence
2517-24	71	TAT GCC GGG TAC TTG TTT CCC GTT CCC GTG GGA ATG CAC TCA CGC TGG TGG AGG CGG TGG GG
2517-25	72	TCG ACC CCA CCG CCT CCT GGA GCG TGA GTG CAT TCC CAC GGG AAG CCG AAA CAA GTA CCC GGC A
2517-26	73	TAT GTG GGG TGC TTG TTG GCC GTT CCC GTG GGA ATG TTT CAA AGA AGG TGG AGG CGG TGG GG
2517-27	74	TCG ACC CCA CCG CCT CCA CCT TCT TTG AAA CAT TCC CACGGG AAC GGC CAA CAAGCA CCC CAC A
2517-28	75	TAT GGT TCC GTT CTG TGA CCT GCT GAC TAA ACA CTG TTT CGA AGC TGG TGG AGG CGG TGG GG
2517-29	76	TCG ACC CCA CCG CCT CCA CCA GCT TCG AAA CAG TGT TTA GTC AGC AGG TCA CAGAAC GGA ACC A
2517-30	77	TAT GGG TTC TCG TTG TAA ATA CAA ATG GGA CGT TCT GAC TAA ACA GTG TTT CCA CCA CGG TGG AGG CGG TGG GG
2517-31	78	TCG ACC CCA CCG CCT CCA CCG TGG TGG AAA CAC TGT TTA GTC AGA ACG TCC CAT TTG TAT TTA CAA CGA GAA CCC A
2517-32	79	TAT GCT GCC GGG TTG TAA ATG GGA CCT GCT GAT CAA ACA GTG GGT TTG TGA CCC GCT GGG TGG AGG CGG TGG GG
2517-33	80	TCG ACC CCA CCG CCT CCA CCC AGC GGG TCA CAA ACC CAC TGT TTG ATC AGC AGG TCC CAT TTA CAA CCC GGC AGC A
2517-34	81	TAT GTC TGC TGA CTG TTA CTT CGA CAT CCT GAC TAA ATC TGA CGT TTG TAC TTC TTC TGG TGG AGG CGG TGG GG
2517-35	82	TCG ACC CCA CCG CCT CCA CCA GAA GAA GTA CAA ACG TCA GAT TTA GTC AGG ATG TCG AAG TAA CAG TCA GCA GAC A
2517-36	83	TAT GTC TGA CGA CTG TAT GTA CGA CCA GCT GAC TCG TAT GTT CAT CTG TTC TAA CCT GGG TGG AGG CGG TGG GG
2517-37	84	TCG ACC CCA CCG CCT CCA CCC AGG TTA GAA CAG ATG AAC ATA CGA GTC AGC TGG TCG TAC ATA CAG TCG TCA GAC A
2521-92	85	TAT GGA CCT GAA CTG TAA ATA CGA CGA ACT GAC TTA CAA AGA ATG GTG TCA GTT CAA CGG TGG AGG CGG TGG GG
25221-93	86	TCG ACC CCA CCG CCT CCA CCG TTG AAC TGA CAC CAT TCT TTG TAA GTC AGTTCG TCG TAT TTA CAG TTC AGG TCC A
2521-94	87	TAT GTT CCA CGA CTG TAA ATA CGA CCT GCT GAC TCG TCA GAT GGT TTG TCA CGG TCT GGG TGG AGG CGG TGG GG
2521-95	88	TCG ACC CCA CCG CCT CCA CCC AGA CCG TGA CAA ACC ATC TGA CGA GTC AGC AGG TCG TAT TTA CAG TCG TGG AAC A
2521-96	89	TAT GCG TAA CCA CTG TTT CTG GGA CCA CCT GCT GAA ACA

		GGA CAT CTG TCC GTC TCC GGG TGG AGG CGG TGG GG
2521-97	90	TCG ACC CCA CCG CCT CCA CCC GGA GAC GGA CAG ATG TCC TGT TTC AGC AGG TGG TCC CAG AAA CAG TGG TTA CGC A
2521-98	91	TAT GGC TAA CCA GTG TTG GTG GGA CTC TCT GCT GAA AAA AAA CGT TTG TGA ATT CTT CGG TGG AGG CGG TGG GG
2521-99	92	TCG ACC CCA CCG CCT CCA CCG AAG AAT TCA CAA ACG TTT TTT TTC AGC AGA GAG TCC CAC CAA CAC TGG TTA GCC A
2551-48	93	TAT GTT CCA CGA CTG CAA ATG GGA CCT GCT GAC CAA ACA GTG GGT TTG CCA CGG TCT GGG TGG AGG CGG TGG GG
2551-49	94	TCG ACC CCA CCG CCT CCA CCC AGA CCG TGG CAA ACC CAC TGT TTG GTC AGC AGG TCC CAT TTG CAG TCG TGG AAC A

pAMG21-RANK-Fc vector

pAMG21. The expression plasmid pAMG21 (ATCC accession no. 98113) can be derived from the Amgen expression vector pCFM1656 (ATCC #69576) which in turn be derived from the Amgen expression vector system described in US Patent No. 4,710,473. The pCFM1656 plasmid can be derived from the described pCFM836 plasmid (U.S. Patent No. 4,710,473) by:

- destroying the two endogenous NdeI restriction sites by end filling with T4 polymerase enzyme followed by blunt end ligation;
- replacing the DNA sequence between the unique AatII and ClaI restriction sites containing the synthetic P_L promoter with a similar fragment obtained from pCFM636 (patent No. 4,710,473) containing the P_L promoter (see SEQ ID NO: 95 below); and
- substituting the small DNA sequence between the unique ClaI and KpnI restriction sites with the oligonucleotide having the sequence of SEQ ID NO: 96.

SEQ ID NO: 95:

AatII
5' CTAATTCGCTCTCACCTACCAAACAATGCCCCCTGCAAAAAATAAATTCATAT-
20 3' TGCAGATTAAGGCGAGAGTGGATGGTTTGTACGGGGGGACGTTTTTTATTTAAGTATA-

-AAAAAACATACAGATAACCATCTGCGGTGATAAATTATCTCTGGCGGTGTTGACATAAA-
-TTTTTTGTATGTCTATTGGTAGACGCCACTATTTAATAGAGACCGCCACAACGTGATTT-

25 -TACCACTGGCGGTGATACTGAGCACAT 3'
-ATGGTGACCGCCACTATGACTCGTGTAGC 5'
ClaI

SEQ ID NO: 96:

5' CGATTTGATTCTAGAAGGAGGAATAACATATGGTTAACGCGTTGGAATTCGGTAC
 3' TAAACTAAGATCTTCCTCCTTATTGTATACCAATTGCGCAACCTTAAGC 5'
ClaI KpnI

5

The expression plasmid pAMG21 can then be derived from pCFM1656 by making a series of site-directed base changes by PCR overlapping oligonucleotide mutagenesis and DNA sequence substitutions. Starting with the BglII site (plasmid bp # 180) immediately 5' to the plasmid replication promoter P_{copB} and proceeding toward the plasmid replication genes, the base pair changes are as shown in Table 7 below.

10

Table 7—Base pair changes resulting in pAMG21

	<u>pAMG21 bp #</u>	<u>bp in pCFM1656</u>	<u>bp changed to in pAMG21</u>
15	# 204	T/A	C/G
	# 428	A/T	G/C
	# 509	G/C	A/T
	# 617	--	insert two G/C bp
20	# 679	G/C	T/A
	# 980	T/A	C/G
	# 994	G/C	A/T
	# 1004	A/T	C/G
	# 1007	C/G	T/A
25	# 1028	A/T	T/A
	# 1047	C/G	T/A
	# 1178	G/C	T/A
	# 1466	G/C	T/A
	# 2028	G/C	bp deletion
30	# 2187	C/G	T/A
	# 2480	A/T	T/A
	# 2499-2502	<u>AGTG</u> <u>TCAC</u>	<u>GTCA</u> <u>CAGT</u>
35	# 2642	<u>TCCGAGC</u> <u>AGGCTCG</u>	7 bp deletion
	# 3435	G/C	A/T
40	# 3446	G/C	A/T
	# 3643	A/T	T/A

The DNA sequence between the unique AatII (position #4364 in pCFM1656) and SacII (position #4585 in pCFM1656) restriction sites is substituted with the DNA sequence below (SEQ ID NO: 97):.

45

[AatII sticky end] 5' GCGTAACGTATGCATGGTCTCC-
(position #4358 in pAMG21) 3' TGCACGCATTGCATACGTACCAGAGG-

5 -CCATGCGAGAGTAGGGAACTGCCAGGCATCAAATAAAACGAAAGGCTCAGTCGAAAGACT-
-GGTACGCTCTCATCCCTTGACGGTCCGTAGTTTATTTTGCTTTCCGAGTCAGCTTTCTGA-

-GGGCCTTTCGTTTTATCTGTTGTTTGTGCGGTGAACGCTCTCCTGAGTAGGACAAATCCGC-
-CCCGGAAAGCAAAATAGACAACAAACAGCCACTTGCGAGAGGACTCATCCTGTTTAGGCG-

10 -CGGGAGCGGATTTGAACGTTGCGAAGCAACGGCCCGGAGGGTGGCGGGCAGGACGCCCCG-
-GCCCTCGCCTAAACTTGCAACGCTTCGTTGCCGGGCCTCCACCGCCCGTCTGCGGGCG-

-CATAAACTGCCAGGCATCAAATTAAGCAGAAGGCCATCCTGACGGATGGCCTTTTTTGCGT-
15 -GTATTGACGGTCCGTAGTTTAATTGCTCTTCCGGTAGGACTGCCTACCGGAAAAACGCA-

-TTCTACAACTCTTTTGTTTATTTTTCTAAATACATTCAAATATGGACGTCGTACTTAAC-
- AatII
-AAGATGTTTGAGAAAAACAAATAAAAAGATTTATGTAAGTTTATACCTGCAGCATGAATTG-

20 -TTTTAAAGTATGGGCAATCAATTGCTCCTGTTAAATTGCTTTAGAAATACCTTTGGCAGC-
-AAAATTTCATACCCGTTAGTTAACGAGGACAATTTTAACGAAATCTTTATGAAACCGTCG-

-GGTTTGTTGTATTGAGTTTCATTTGCGCATTGGTTAAATGGAAAGTGACCGTGCGCTTAC-
25 -CCAAACAACATAACTCAAAGTAAACGCGTAACCAATTTACCTTTCACTGGCACGCGAATG-

-TACAGCCTAATATTTTTGAAATATCCCAAGAGCTTTTTCCTTCGCATGCCCACGCTAAAC-
-ATGTCGGATTATAAAAACTTTATAGGGTCTCGAAAAAGGAAGCGTACGGGTGCGATTTG-

-ATTCTTTTTCTCTTTTGTTAAATCGTTGTTTGATTTATTATTTGCTATATTTATTTTTC-
30 -TAAGAAAAAGAGAAAACCAATTTAGCAACAACTAAATAATAACGATATAAATAAAAAAG-

-GATAATTATCAACTAGAGAAGGAACAATTAATGGTATGTTTCATACACGCATGTAAAAATA-
-CTATTAATAGTTGATCTCTTCCTTGTTAATTACCATACAAGTATGTGCGTACATTTTTAT-

35 -AACTATCTATATAGTTGTCTTTCTCTGAATGTGCAAACTAAGCATTCCGAAGCCATTAT-
-TTGATAGATATATCAACAGAAAGAGACTTACACGTTTTGATTTCGTAAGGCTTCGGTAATA-

-TAGCAGTATGAATAGGGAACTAAACCCAGTGATAAGACCTGATGATTTGCTTCTTTAA-
40 -ATCGTCATACTTATCCCTTTGATTTGGGTCACTATTCTGGACTACTAAAGCGAAGAAATT-

-TTACATTTGGAGATTTTTTATTTACAGCATTGTTTTCAAATATATTCCAATTAATCGGTG-
-AATGTAAACCTCTAAAAATAAATGTCGTAACAAAAGTTTATATAAGGTTAATTAGCCAC-

-AATGATTGGAGTTAGAATAATCTACTATAGGATCATATTTTATTAAATTAGCGTCATCAT-
45 -TTACTAACCTCAATCTTATTAGATGATATCCTAGTATAAAATAATTTAATCGCAGTAGTA-

-AATATTGCCTCCATTTTTTAGGGTAATTATCCAGAATTGAAATATCAGATTTAACCATAG-
-TTATAACGGAGGTAAAAATCCCATTAATAGGCTTAACTTTATAGTCTAAATTGGTATC-

50 -AATGAGGATAAATGATCGCGAGTAAATAATATTCACAATGTACCATTTTAGTCATATCAG-
-TTACTCCTATTTACTAGCGCTCATTTATTATAAGTGTTACATGGTAAATCAGTATAGTC-

-ATAAGCATTGATTAATATCATTATTGCTTCTACAGGCTTTAATTTTATTAATTATTCTGT-
55 -TATTCGTAACATAATTATAGTAATAACGAAGATGTCCGAAATTAAAAATAATTAATAAGACA-

-AAGTGTGCTCGGCATTTATGTCTTTCATACCCATCTCTTTATCCTTACCTATTGTTTGTC-
-TTCACAGCAGCCGTAAATACAGAAAGTATGGGTAGAGAAATAGGAATGGATAACAAACAG-

-GCAAGTTTTGCGTGTTATATATCATTAACGGAATAGATTGACATTTGATTCTAATAA-
60 -CGTTCAAAACGCACAATATATAGTAATTTTGCCATTATCTAACTGTAAACTAAGATTATT-

-ATTGGATTTTTGTACACTATTATATCGCTTGAAATACAATTGTTTAACATAAGTACCTG-
-TAACCTAAAAACAGTGTGATAATATAGCGAAGTTTATGTTAACAAATTGTATTTCATGGAC-

-TAGGATCGTACAGGTTTACGCAAGAAAATGGTTTGTATAGTCGATTAATCGATTTGATT-
 -ATCCTAGCATGTCCAAATGCGTTCTTTTACCAAACAATATCAGCTAATTAGCTAAACTAA-
 5 -CTAGATTTGTTTTAACTAATTAAAGGAGGAATAACATATGGTTAACGCGTTGGAATTCGA-
 -GATCTAAACAAAATTGATTAATTTCTCCTTATTGTATACCAATTGCGCAACCTTAAGCT-

 -GCTCACTAGTGTGACCTGCAGGGTACCATGGAAGCTTACTCGAGGATCCGCGGAAAGAA-
 10 -CGAGTGATCACAGCTGGACGTCCCATGGTACCTTCGAATGAGCTCCTAGGCGCCTTTCTT-
 -GAAGAAGAAGAAGAAAGCCCCGAAAGGAAGCTGAGTTGGCTGCTGCCACCGCTGAGCAATA-
 -CTTCTTCTTCTTCTTTCGGGCTTTCCTTCGACTCAACCGACGACGGTGGCGACTCGTTAT-
 15 -ACTAGCATAACCCCTTGGGGCTCTAAACGGGTCTTGAGGGGTTTTTTGCTGAAAGGAGG-
 -TGATCGTATTGGGGAACCCCGGAGATTGCCCCAGAACTCCCCAAAAACGACTTTCCTCC-

 -AACCGCTCTTCACGCTCTTCACGC 3' [SacII sticky end]
 -TTGGCGAGAAGTGCGAGAAGTG 5' (position #5904 in pAMG21)

20 During the ligation of the sticky ends of this substitution DNA sequence, the outside AatII and SacII sites are destroyed. There are unique AatII and SacII sites in the substituted DNA.

A gene encoding human RANK fused to the N-terminus of Fc was ligated into pAMG21 as an NdeI to BamHI fragment to generate Amgen Strain #4125. This
 25 construct was modified to insert a valine codon at the junction of RANK and Fc. The adjacent valine and aspartate codons create a unique SalI site. This allows for the fusion of peptides at the N-terminus of Fc3 between the unique NdeI and SalI sites. The RANK sequence is deleted upon insertion of a new NdeI-SalI fragment. The sequence of the vector is given in Figure 5A through 5M.

30 GM221 (Amgen #2596). The Amgen host strain #2596 is an E. coli K-12 strain derived from Amgen strain #393, which is a derivative of E. coli W1485, obtained from the E. coli Genetic Stock Center, Yale University, New Haven, Connecticut (CGSC strain 6159). It has been modified to contain both the temperature sensitive lambda repressor cI857s7 in the early ebg region and the
 35 lacI^Q repressor in the late ebg region (68 minutes). The presence of these two repressor genes allows the use of this host with a variety of expression systems, however both of these repressors are irrelevant to the expression from luxP_R. The untransformed host has no antibiotic resistances.

The ribosome binding site of the cI857s7 gene has been modified to
 40 include an enhanced RBS. It has been inserted into the ebg operon between

nucleotide position 1170 and 1411 as numbered in Genbank accession number M64441Gb_Ba with deletion of the intervening ebg sequence. The sequence of the insert is shown below with lower case letters representing the ebg sequences flanking the insert shown below (SEQ ID NO: 98):

5
 10
 15
 20
 ttatttcgtGCGGCCGCACCATTTATCACCGCCAGAGGTAACTAGTCAACACGCACGGTGTTAGATAT
 TTATCCCTTGCGGTGATAGATTGAGCACATCGATTTGATTCTAGAAGGAGGGATAATATATGAG
 CACAAAAAAGAAACCATTAACACAAGAGCAGCTTGAGGACGCACGTCGCCTTAAAGCAATTTA
 TGAAAAAAGAAAAATGAACTTGGCTTATCCCAGGAATCTGTGCGAGACAAGATGGGGATGGG
 GCAGTCAGGCGTTGGTGCTTTATTTAATGGCATCAATGCATTAAATGCTTATAACGCCGCATTGC
 TTACAAAAATTTCTCAAAGTTAGCGTTGAAGAATTTAGCCCTTCAATCGCCAGAGAATCTACGAG
 ATGTATGAAGCGGTTAGTATGCAGCCGTCACCTAGAAAGTGAGTATGAGTACCCTGTTTTTCTCA
 TGTTTCAGGCAGGGATGTTCTCACCTAAGCTTAGAACCTTTACCAAAGGTGATGCGGAGAGATGG
 GTAAGCACAAACAAAAAGCCAGTGATTCTGCATTCTGGCTTGAGGTTGAAGGTAATTCCATGA
 CCGCACCAACAGGCTCCAAGCCAAGCTTTCTGACGGAATGTTAATTCTCGTTGACCCTGAGCA
 GGCTGTTGAGCCAGGTGATTTCTGCATAGCCAGACTTGGGGGTGATGAGTTTACCTTCAAGAAA
 CTGATCAGGGATAGCGGTCAGGTGTTTTTACAACCACTAAACCCACAGTACCCAATGATCCCAT
 GCAATGAGAGTTGTTCCGTTGTGGGGAAAGTTATCGCTAGTCAGTGGCCTGAAGAGACGTTTGG
 CTGATAGACTAGTGGATCCACTAGTgtttctgccc

The construct was delivered to the chromosome using a recombinant phage called MMeBg-cI857s7enhanced RBS #4 into F'tet/393. After recombination and resolution only the chromosomal insert described above remains in the cell. It was renamed F'tet/GM101. F'tet/GM101 was then modified
 25 by the delivery of a lacI^Q construct into the ebg operon between nucleotide position 2493 and 2937 as numbered in the Genbank accession number M64441Gb_Ba with the deletion of the intervening ebg sequence. The sequence of the insert is shown below with the lower case letters representing the ebg sequences flanking the insert (SEQ ID NO: 99) shown below:

30
 35
 40
 45
 ggcggaaccGACGTCCATCGAATGGTGCAAAACCTTTTCGCGGTATGGCATGATAGCGCCCGGAAGA
 GAGTCAATTCAGGGTGGTGAATGTGAAACAGTAACGTTATACGATGTGCGAGAGTATGCCGGT
 GTCTCTTATCAGACCGTTTCCCGCGTGGTGAACCAGGCCAGCCACGTTTCTGCGAAAACGCGGG
 AAAAAGTCGAAGCGGCGATGGCGGAGCTGAATTACATTCCCAACCGCGTGGCACAACAATGG
 CGGGCAAACAGTCGCTCCTGATTGGCGTTGCCACCTCCAGTCTGGCCCTGCACGCGCCGTCGCA
 AATTGTCGCGGCGATTAAATCTCGCGCCGATCAACTGGGTGCCAGCGTGCTGGTGTCGATGGTA
 GAACGAAGCGGCGTCGAAGCCTGTAAGCGGCGGTGCACAATCTTCTCGCGCAACGCGTCAGTG
 GGCTGATCATTAACATCCGCTGGATGACCAGGATGCCATTGCTGTGGAAGCTGCCTGCACTAA
 TGTTCCGGCGTTATTTCTTGATGTCTCTGACCAGACACCCATCAACAGTATTATTTTCTCCCATGA
 AGACGGTACGCGACTGGGCGTGGAGCATCTGGTTCGATTGGGTCAACAGCAATCGCGCTGTTA
 GCGGGCCCCATTAAGTTCTGTCTCGGCGCGTCTGCGTCTGGCTGGCTGGCATAAATATCTCACTCG
 CAATCAAAATTCAGCCGATAGCGGAACGGGAAGGCGACTGGAGTGCCATGTCCGGTTTTCAACAA
 ACCATGCAAAATGCTGAATGAGGGCATCGTTCCTCCCATGCGATGCTGGTTGCCAACGATCAGATGG
 CGCTGGGCGCAATGCGCGCCATTACCGAGTCCGGGCTGCGCGTTGGTGCGGATATCTCGGTAGT
 GGGATACGACGATAAAGACAGCTCATGTTATATCCCGCGTTAACCACCATCAACAGGAT
 TTTGCGCTGCTGGGGCAACAGCGTGGACCGCTTGTGCAACTCTCTCAGGGCCAGGCGGTGA

AGGGCAATCAGCTGTTGCCCCGTCTCACTGGTGAAAAGAAAAACCACCCTGGCGCCCAATACGCA
 AACCGCCTCTCCCCGCGCGTTGGCCGATTCAATTAATGCAGCTGGCACGACAGGTTTCCCGACTGG
 AAAGCGGACAGTAAGGTACCATAGGATCCaggcacagga

5 The construct was delivered to the chromosome using a recombinant
 phage called AGebg-LacIQ#5 into F'tet/GM101. After recombination and
 resolution only the chromosomal insert described above remains in the cell. It
 was renamed F'tet/GM221. The F'tet episome was cured from the strain using
 acridine orange at a concentration of 25 µg/ml in LB. The cured strain was
 10 identified as tetracycline sensitive and was stored as GM221.

Expression in *E. coli*. Cultures of each of the pAMG21-Fc-fusion
 constructs in *E. coli* GM221 were grown at 37 °C in Luria Broth medium.
 Induction of gene product expression from the luxPR promoter was achieved
 15 following the addition of the synthetic autoinducer N-(3-oxohexanoyl)-DL-
 homoserine lactone to the culture media to a final concentration of 20 ng/ml.
 Cultures were incubated at 37 °C for a further 3 hours. After 3 hours, the bacterial
 cultures were examined by microscopy for the presence of inclusion bodies and
 were then collected by centrifugation. Refractile inclusion bodies were observed
 20 in induced cultures indicating that the Fc-fusions were most likely produced in the
 insoluble fraction in *E. coli*. Cell pellets were lysed directly by resuspension in
 Laemmli sample buffer containing 10% β-mercaptoethanol and were analyzed by
 SDS-PAGE. In each case, an intense Coomassie-stained band of the appropriate
 molecular weight was observed on an SDS-PAGE gel.

25

EXAMPLE 3

TALL-1 peptibody inhibits TALL-1 mediated B cell proliferation

Mouse B lymphocytes were isolated from C57BL/6 spleens by negative
 selection. (MACS CD43 (Ly-48) Microbeads, Miltenyi Biotech, Auburn, CA).
 30 Purified (10^5) B cells were cultured in MEM, 10% heat inactivated FCS, 5×10^{-5} M
 2-mercaptoethanol, 100 U/ml penicillin, 100 µg/ml streptomycin) in triplicate in
 96-well flat bottom tissue culture plates with 10 ng/ml TALL-1 protein and 2
 µg/ml of Goat F(ab')₂ anti-mouse IgM (Jackson ImmunoResearch Laboratory,

West Grove, Pennsylvania) with the indicated amount of recombinant TALL-1 peptibody for a period of 4 days at 37 °C, 5%CO₂. Proliferation was measured by the uptake of radioactive ³[H] thymidine after an 18-hour incubation period.

5

EXAMPLE 4

TALL-1 peptibody blocks TALL-1 binding to its receptors

Reacti-Gel 6x (Pierce) were pre-coated with human AGP3 (also known as TALL-1, Khare et al., Proc. Natl. Acad. Sci. 97:3370-3375, 2000) and blocked
10 with BSA. 100 pM and 40 pM of AGP3 peptibody samples were incubated with indicated various concentrations of human AGP3 at room temperature for 8 hours before run through the human AGP3-coated beads. The amount of the bead-bound peptibody was quantified by fluorescent (Cy5) labeled goat anti-human-Fc antibody (Jackson Immuno Research). The binding signal is proportional to the
15 concentration of free peptibody at binding equilibrium. Dissociation equilibrium constant (K_D) was obtained from nonlinear regression of the competition curves using a dual-curve one-site homogeneous binding model (KinEx™ software). K_D is about 4 pM for AGP3 peptibody (SEQ ID NO: 123) binding with human AGP3 (Figure 10).

20 To determine if this AGP3 peptibody can neutralize murine AGP3 binding as well as human AGP3, a BIAcore neutralizing assay was utilized. All experiments were performed on a BIAcore 3000 at room temperature. Human TACI-Fc protein (Xia et al, J. Exp. Med. 192, 137-144, 2000) was immobilized to a B1 chip using 10 mM Acetate pH 4.0 to a level of 2900RU. A blank flow cell
25 was used as a background control. Using a running buffer of PBS (without calcium or magnesium) containing 0.005% P20, 1 nM recombinant human AGP3 (in running buffer plus, 0.1 mg/ml BSA) was incubated without and with indicated various amount of AGP3 peptibody (x axis) before injected over the surface of the receptor. Regeneration was performed using 8 mM glycine pH 1.5 for 1 minute,
30 25 mM 3-[cyclohexylamino]-1-propanesulfonic acid (CAPS) pH 10.5, 1 M NaCl for 1 minute. For determination of murine AGP3 binding, human his-tagged

TACI was immobilized to 1000 RU in the above buffer. 5 nM recombinant murine AGP3 (in running buffer plus, 0.1 mg/ml BSA) was incubated without and with the various amounts indicated in Figure 11 of AGP3 peptibody (x axis) before injected over the surface of the receptor. Regeneration was performed with 10 mM HCl pH2, twice for 30 seconds. Relative binding of both human and murine AGP3 at presence vs absence of AGP3 peptibody (SEQ ID NO: 123) was measured (y axis). Relative binding response was determined as (RU-RU blank/RUo-RU blank). The AGP3 peptibody (SEQ ID NO: 123) inhibited both human and murine AGP3 binding to its receptor TACI (Figures 11A and 11B).

To examine if this AGP3 peptibody blocks AGP3 binding to all three receptors (TACI, BCMA and BAFFR), recombinant soluble receptor TACI, BCMA and BAFFR proteins were immobilized to CM5 chip. Using 10 mM acetate, pH4, human TACI-Fc was immobilized to 6300 RU, human BCMA-Fc to 5000 RU, and BAFFR-Fc to 6000 RU. 1 nM of recombinant human AGP3 (in running buffer containing 0.1 mg/ml BSA and 0.1 mg/ml Heparin) or 1 nM recombinant APRIL protein (Yu, et al., Nat. Immunol., 1:252-256, 2000) were incubated with indicated amount of AGP3 peptibody before injection over each receptor surface. Regeneration for the AGP3 experiment was done with 8 mM glycine, pH 1.5, for 1 minute, followed by 25 mM CAPS, pH 10.5, 1M NaCl for 1 minute. Regeneration for the APRIL experiment was performed with 8 mM glycine, pH 2, for one minute, followed by 25 mM CAPS, pH 10.5, 1 M NaCl for one minute. Relative binding of AGP3 or APRIL was measured. AGP3 peptibody (SEQ ID NO: 123) blocked AGP3 binding to all three receptors (Figure 12A). AGP3 peptibody didn't affect APRIL binding to the receptors (Figure 12B).

EXAMPLE 5

AGP3 peptibody blocks AGP3 mediated B cell proliferation

Mouse B lymphocytes were isolated from C57BL/6 spleens by negative selection. (MACS CD43 (Ly-48) Microbeads, Miltenyi Biotech, Auburn, CA).

Purified (10^5) B cells were cultured in minimal essential medium (MEM), 10% heat inactivated fetal calf serum (FCS), 5×10^{-5} M 2-mercaptoethanol, 100 U/ml penicillin, 100 μ g/ml streptomycin) in triplicate in 96-well flat bottom tissue culture plates with 10 ng/ml AGP3 (TALL-1) protein and 2 μ g/ml of Goat F(ab')₂ anti-mouse IgM (Jackson ImmunoResearch Laboratory, West Grove, Pennsylvania) with the indicated amount of recombinant AGP3 peptibody (SEQ ID NO: 123) for a period of 4 days at 37 °C, 5% CO₂. Proliferation was measured by the uptake of radioactive ³[H] thymidine after an 18-hour incubation period.

10

EXAMPLE 6

AGP3 peptibody on AGP3-stimulated Ig production in mice

Mice (Balb/c females of 9-14 weeks of age and 19-21 g of weight) were purchased from Charles River Laboratories, Wilmington, MA. Mice (n = 10) were treated i.p. with 1 mg/Kg of human AGP3 once a day for five consecutive days followed by 5 mg/Kg or 0.5 mg/Kg of AGP3 peptibody (SEQ ID NO: 123) or by saline or by 5 mg/Kg of human Fc. Other mice were left untreated. Mice were sacrificed on the sixth day to measure serum IgM and IgA, which were measured by ELISA. Briefly, plates were coated with capture antibodies specific for IgM or IgA (Southern Biotechnology Associates, Birmingham, AL), blocked, and added with dilutions of standard (IgM from Calbiochem, San Diego, CA and IgA from Southern Biotechnology Associates) or test samples. Captured Ig were revealed using biotinylated antibodies specific for IgM or IgA (Southern Biotechnology Associates), neutravidin-conjugated peroxidase (Pierce, Rockford, IL), and tetramethylbenzidine (TMB) microwell peroxidase substrate (KPL, Gaithersburg, MD). Optical densities were quantitated in a Thermomax ELISA reader (Molecular Devices, Menlo Park, CA).

Human AGP3-stimulated increase in serum levels of IgM and IgA was blocked by 5 mg/Kg of the anti-AGP3 peptibody (SEQ ID NO: 123) and not by 0.5 mg/Kg (Figures 14A and 14B).

EXAMPLE 7

AGP3 peptibody reduced spleen B cell number in mice

Mice (as above, n = 7) were treated i.p. for seven consecutive days with 5
5 mg/Kg or 1.5 mg/Kg or 0.5 mg/Kg of AGP3 peptibody (SEQ ID NO: 123) or with
saline or with 5 mg/Kg of human Fc. Mice were sacrificed on the eighth day to
count spleen B cell number. Spleens were collected in saline and gently disrupted
by manual homogenization to yield a cell suspension. The total cell number was
obtained with a HIE counter (Technicon, Tarrytown, NY). Percentages of B cells
10 were derived by immunofluorescence double staining and flow cytometry using
fluorescein isothiocyanate (FITC)-conjugated and phycoerythrin (PE)-
conjugated Ab against CD3 and B220, respectively (PharMingen, San Diego,
CA) and a FACScan analyser (Becton and Dickinson, Mountain View, CA). B
cells were identified for being CD3-B220+. At all doses, the AGP3 peptibody
15 (SEQ ID NO: 123) decreased spleen B cell number in a dose-response fashion
(Figure 14) (SEQ ID NO: 123).

EXAMPLE 8

AGP3 peptibody reduced arthritis severity in mouse CIA model

20 Eight to 12 week old DBA/1 mice (obtained from Jackson Laboratories,
Bar Harbor, ME) were immunized with bovine collagen type II (bCII) (purchased
from University of Utah), emulsified in complete Freund's adjuvant (Difco)
intradermally at the base of tail. Each injection was 100 µl containing 100 µg of
25 bCII. Mice were boosted 3 weeks after the initial immunization with bCII
emulsified in incomplete Freund's adjuvant. Treatment was begun from the day of
booster immunization for 4 weeks. Mice were examined for the development of
arthritis. As described before (Khare et al., *J. Immunol.* 155: 3653-9, 1995), all
four paws were individually scored from 0-3. Therefore arthritis severity could
30 vary from 0 to 12 for each animal. AGP3 (SEQ ID NO: 123) peptibody treatment
significantly reduced the severity of arthritic scores (Figure 15).

Serum samples were taken one week after final treatment (day 35) for the analysis of anti-collagen antibody level. High binding ELISA plates (Immulon, Nunc) were coated with 50 μ l of 4 μ g/ml solution of bovine CII in carbonate buffer and plated were kept in cold overnight in the refrigerator. Plates were washed three times with cold water. 75 μ l of blocking solution made up of PBS/.05% tween 20/1% BSA was used to block non-specific binding for an hour. Samples were diluted (in blocking buffer) in dilution plates at 1:25, 1:100, 1:400, and 1:1600 and 25 μ l of these samples were added to each well of the ELISA plate for a final dilution of 100, 400, 1600, and 6400 with a final volume of 100 μ l/well. After incubation at room temperature for 3 hours, plates were washed three times again. 100 μ l of secondary antibody diluted in blocking buffer (rat anti-mouse IgM, IgG2a, IgG2b, IgG1, IgG3-HRP) was added to each well and plates were incubated for at least 2 hours. Plates were washed four times. 100 μ l of TMB solution (Sigma) was added to each well and the reaction was stopped using 50 μ l of 25% sulfuric acid. Plates were read using an ELISA plate reader at 450 nm. OD was compared with a standard pool representing units/ml. AGP3 peptibody (SEQ ID NO: 123) treatment reduced serum anti-collagen II IgG1, IgG3, IgG2a, and IgG2b levels compared to PBS or Fc control treatment groups (Figure 16).

EXAMPLE 9

Treatment of AGP3 peptibody in NZB/NZW lupus mice

Five month old lupus prone NZBx NZBWF1 mice were treated i.p. 3X/week for 8 weeks with PBS or indicated doses of AGP3 peptibody or human Fc proteins. Prior to the treatment, animals were pre-screened for protein in the urine with Albustix reagents strips (Bayer AG). Mice having greater than 100 mg/dl of protein in the urine were not included in the study. Protein in the urine was evaluated monthly throughout the life of the experiment. AGP3 peptibody (SEQ ID NO: 123) treatment led to delay of proteinuria onset and improved survival (Figure 17).

AGP3 peptibody treatment reduced B cell number in mice. Balb/c mice received 7 daily intraperitoneal injections of indicated amount of AGP3 peptibody (SEQ ID NO: 123) or human Fc protein. On day 8, spleens were collected, and subject to FACS analysis for B220+ B cells as set for in Table 8.

5

Table 8
AGP3 Pb Reduces B Cell Number in Normal Mice

n=7	dose (1/dayx7)	spleen B cell (1x10e6)	SD	t test
saline		51.3	9.6	
Fc	5mg/Kg	45.5	7.1	
Peptibody	5mg/Kg	20.1	3.8	1.37856E-05
	1.5mg/Kg	22.6	6.9	5.10194E-05
	0.5mg/Kg	25.8	3.6	0.000111409

10

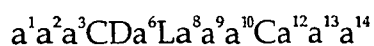
* * *

The invention now being fully described, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto, without departing from the spirit and scope of the invention as set forth herein.

15

What is claimed is:

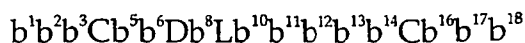
1. A TALL-1-binding composition of matter comprising an amino acid sequence Dz^2Lz^4 , wherein z^2 is an amino acid residue and z^4 is T or I,
 5 and wherein the composition of matter does not comprise a fragment of TACI, BCMA, or BAFFR (SEQ ID NOS: 195, 196, and 197).
2. The composition of matter of Claim 1, wherein z^4 is T.
3. A TALL-1-binding composition of matter comprising an amino acid sequence Dz^2LI , wherein z^2 is an amino acid residue.
- 10 4. The composition of matter of Claim 1 comprising an amino acid sequence of the formula



(SEQ. ID. NO: 100)

wherein:

- 15 a^1, a^2, a^3 are each independently absent or amino acid residues;
 a^6 is an amino acid residue;
 a^8 is T or I;
 a^9 is a basic or hydrophobic residue;
 a^{12} is a neutral polar residue; and
 20 a^{13} and a^{14} are each independently absent or amino acid residues.
5. The composition of matter of Claim 4 wherein a^8 is T and a^9 is a basic residue.
6. The composition of matter of Claim 4 wherein a^9 is K and a^{12} is F.
7. The composition of matter of Claim 1 comprising an amino acid
 25 sequence of the formula



(SEQ. ID. NO: 104)

wherein:

- b^1 and b^2 are each independently absent or amino acid residues;
 30 b^3 is an acidic or amide residue;

b⁵ is an amino acid residue;

b⁶ is an aromatic residue;

b⁸ is an amino acid residue;

b¹⁰ is T or I;

5 b¹¹ is a basic residue;

b¹² and b¹³ are each independently amino acid residues;

b¹⁴ is a neutral polar residue; and

b¹⁶, b¹⁷, and b¹⁸ are each independently absent or amino acid residues.

10 8. The composition of matter of Claim 7 wherein:

b³ is D, Q, or E;

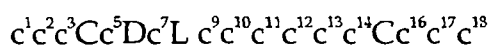
b⁶ is W or Y;

b¹⁰ is T;

b¹¹ is K or R; and

15 b¹⁴ is V or L.

9. The composition of matter of Claim 1 comprising an amino acid sequence of the formula



(SEQ. ID. NO: 105)

20 wherein:

c¹, c², and c³ are each independently absent or amino acid residues;

c⁵ is an amino acid residue;

c⁷ is an amino acid residue;

c⁹ is T or I;

25 c¹⁰ is a basic residue;

c¹¹ and c¹² are each independently amino acid residues;

c¹³ is a neutral polar residue;

c¹⁴ is an amino acid residue;

c¹⁶ is an amino acid residue;

30 c¹⁷ is a neutral polar residue; and

c^{18} is an amino acid residue or is absent.

10. The composition of matter of Claim 9 wherein:

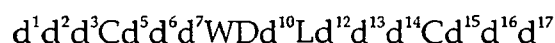
c^9 is T;

c^{10} is K or R;

5 c^{13} is a I, L, or V; and

c^{17} is A or L.

11. The composition of matter of Claim 1 comprising an amino acid sequence of the formula



10 (SEQ. ID. NO: 106)

wherein:

d^1 , d^2 , and d^3 are each independently absent or amino acid residues;

d^5 , d^6 , and d^7 are each independently amino acid residues;

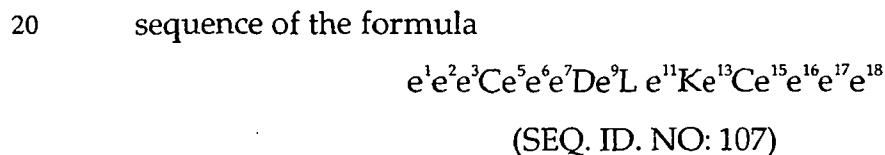
d^{10} is an amino acid residue;

15 d^{13} is T or I;

d^{14} is an amino acid residue; and

d^{16} , d^{17} , and d^{18} are each independently absent or amino acid residues.

12. The composition of matter of Claim 1 comprising an amino acid sequence of the formula



wherein:

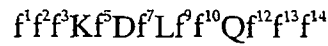
e^1 , e^2 , and e^3 are each independently absent or amino acid residues;

25 e^5 , e^6 , e^7 , e^9 , and e^{13} are each independently amino acid residues;

e^{11} is T or I; and

e^{15} , e^{16} , and e^{17} are each independently absent or amino acid residues.

13. The composition of matter of Claim 1 comprising an amino acid sequence of the formula



(SEQ ID NO: 109)

5 wherein:

f^1 , f^2 , and f^3 are absent or are amino acid residues;

f^5 is W, Y, or F;

f^7 is an amino acid residue;

f^9 is T or I;

10 f^{10} is K, R, or H;

f^{12} is C, a neutral polar residue, or a basic residue (W, C, or R preferred);

f^{13} is C, a neutral polar residue or is absent; and

f^{14} is any amino acid residue or is absent;

15 provided that only one of f^1 , f^2 , and f^3 may be C, and only one of f^{12} , f^{13} , and f^{14} may be C.

14. The composition of matter of Claim 13, wherein f^5 is W.

15. The composition of matter of Claim 13, wherein f^7 is L.

16. The composition of matter of Claim 13, wherein f^9 is T.

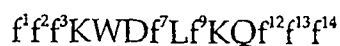
20 17. The composition of matter of Claim 13, wherein f^{10} is K.

18. The composition of matter of Claim 13, wherein f^{12} is C and one of f^1 , f^2 , and f^3 is C.

19. The composition of matter of Claim 13, wherein f^{13} is V.

20. The composition of matter of Claim 13 comprising an amino acid

25 sequence of the formula



(SEQ ID NO: 125).

21. The composition of matter of Claim 20 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 32, 33, 58,

60, 63, 66, 67, 69, 114, 115, 122, 123, 124, 147-150, 152-177, 179, 180, and 187.

22. The composition of matter of Claim 20 comprising an amino acid
5 sequence of the formula

LPGCKWDLLIKQWVCDPL (SEQ ID NO: 33).

23. A composition of matter comprising an amino acid sequence of the
formula

$$g^1 g^2 g^3 C g^5 P F g^8 W g^{10} C g^{11} g^{12} g^{13}$$

(SEQ. ID. NO: 101)

wherein:

g^1 , g^2 and g^3 are each independently absent or amino acid residues;

g^5 is a neutral polar residue;

g^8 is a neutral polar residue;

15 g^{10} is an acidic residue;

g^{12} and g^{13} are each independently amino acid residues; and

g^{14} is absent or is an amino acid residue.

24. The composition of matter of Claim 23 wherein:

g^2 is G;

20 g^5 is W;

g^8 is P;

g^{10} is E; and

g^{13} is a basic residue.

25. A composition of matter comprising an amino acid sequence of the
25 formula

$$h^1 h^2 h^3 C W h^6 h^7 W G h^{10} C h^{12} h^{13} h^{14}$$

(SEQ. ID. NO: 102)

wherein:

h^1 , h^2 , and h^3 are each independently absent or amino acid residues;

30 h^6 is a hydrophobic residue;

h^7 is a hydrophobic residue;

h^{10} is an acidic or polar hydrophobic residue; and

h^{12} , h^{13} , and h^{14} are each independently absent or amino acid residues.

26. The composition of matter of Claim 25 wherein:

5 h^1 is G;

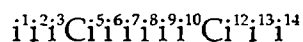
h^6 is A;

h^7 is a neutral polar residue; and

h^{10} is an acidic residue.

27. A composition of matter comprising an amino acid sequence of the

10 formula



(SEQ. ID. NO: 103)

wherein:

i^1 is absent or is an amino acid residue;

15 i^2 is a neutral polar residue;

i^3 is an amino acid residue;

i^5 , i^6 , i^7 , and i^8 are each independently amino acid residues;

i^9 is an acidic residue;

i^{10} is an amino acid residue;

20 i^{12} and i^{13} are each independently amino acid residues; and

i^{14} is a neutral polar residue.

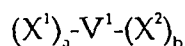
28. The composition of matter of Claim 27 wherein:

i^2 is W; and

i^{14} is W.

25 29. A TALL-1 binding composition of matter comprising an amino acid sequence of the formula PFPWE (SEQ ID NO: 110). :

30. The composition of matter of Claim 1 having the formula



30 and multimers thereof, wherein:

V^1 is a vehicle;

X^1 and X^2 are each independently selected from $-(L^1)_c-P^1$,

$-(L^1)_c-P^1-(L^2)_d-P^2$, $-(L^1)_c-P^1-(L^2)_d-P^2-(L^3)_e-P^3$, and

$-(L^1)_c-P^1-(L^2)_d-P^2-(L^3)_e-P^3-(L^4)_f-P^4$

5 one or more of P^1 , P^2 , P^3 , and P^4 each independently comprise

Dz^2Lz^4 ;

L^1 , L^2 , L^3 , and L^4 are each independently linkers; and

a, b, c, d, e, and f are each independently 0 or 1, provided that at least one of a and b is 1.

10 31. The composition of matter of Claim 30 of the formula

$$P^1-(L^1)_c-P^2-(L^2)_d-V^1.$$

32. The composition of matter of Claim 30 of the formula

$$V^1-(L^1)_c-P^1-(L^2)_d-P^2.$$

15 33. The composition of matter of Claim 30, wherein V^1 is an Fc domain.

34. The composition of matter of Claim 30 wherein V^1 is an IgG Fc domain.

35. The composition of matter of Claim 30 wherein V^1 is an IgG1 Fc domain.

36. The composition of matter of Claim 30 wherein V^1 comprises the
20 sequence of SEQ ID NO: 2.

37. The composition of matter of Claim 30 wherein one or more of P^1 , P^2 , P^3 , and P^4 each independently comprises a sequence selected from:

$a^1a^2a^3CDa^6La^8a^9a^{10}Ca^{12}a^{13}a^{14}$ (SEQ. ID. NO: 100)

$b^1b^2b^3Cb^5b^6Db^8Lb^{10}b^{11}b^{12}b^{13}b^{14}Cb^{16}b^{17}b^{18}$ (SEQ. ID. NO: 104)

25 $c^1c^2c^3Cc^5Dc^7Lc^9c^{10}c^{11}c^{12}c^{13}c^{14}Cc^{16}c^{17}c^{18}$ (SEQ. ID. NO: 105)

$d^1d^2d^3Cd^5d^6d^7WDd^{10}Ld^{13}d^{14}d^{15}Cd^{16}d^{17}d^{18}$ (SEQ. ID. NO: 106)

$e^1e^2e^3Ce^5e^6e^7De^9Le^{11}Ke^{13}Ce^{15}e^{16}e^{17}e^{18}$ (SEQ. ID. NO: 107)

$f^1f^2f^3Kf^5Df^7Lf^9f^{10}Qf^{12}f^{13}f^{14}$ (SEQ. ID. NO: 109)

$g^1 g^2 g^3 Cg^5 PFg^8 Wg^{10} Cg^{11} g^{12} g^{13}$ (SEQ ID NO: 101),
 $h^1 h^2 h^3 CWh^6 h^7 Wgh^{10} Ch^{12} h^{13} h^{14}$ (SEQ ID NO: 102), and
 $i^{1,2,3} Ci^{5,6,7,8,9,10} Ci^{12,13,14}$ (SEQ ID NO: 103)

wherein:

- 5 a^1, a^2, a^3 are each independently absent or amino acid residues;
 a^6 is an amino acid residue;
 a^9 is a basic or hydrophobic residue;
 a^8 is threonyl or isoleucyl;
 a^{12} is a neutral polar residue;
 10 a^{13} and a^{14} are each independently absent or amino acid residues;
 b^1 and b^2 are each independently absent or amino acid residues;
 b^3 is an acidic or amide residue;
 b^5 is an amino acid residue;
 b^6 is an aromatic residue;
 15 b^8 is an amino acid residue;
 b^{10} is T or I;
 b^{11} is a basic residue;
 b^{12} and b^{13} are each independently amino acid residues;
 b^{14} is a neutral polar residue;
 20 b^{16}, b^{17} , and b^{18} are each independently absent or amino acid
 residues;
 c^1, c^2 , and c^3 are each independently absent or amino acid residues;
 c^5 is an amino acid residue;
 c^7 is an amino acid residue;
 25 c^9 is T or I;
 c^{10} is a basic residue;
 c^{11} and c^{12} are each independently amino acid residues;
 c^{13} is a neutral polar residue;
 c^{14} is an amino acid residue;
 30 c^{16} is an amino acid residue;

- c^{17} is a neutral polar residue; and
 c^{18} is an amino acid residue or is absent;
 d^1, d^2 , and d^3 are each independently absent or amino acid residues;
 d^5, d^6 , and d^7 are each independently amino acid residues;
5 d^{10} is an amino acid residue;
 d^{12} is T or I;
 d^{13} is an amino acid residue; and
 d^{15}, d^{16} , and d^{17} are each independently absent or amino acid residues;
10 e^1, e^2 , and e^3 are each independently absent or amino acid residues;
 e^5, e^6, e^7, e^9 , and e^{13} are each independently amino acid residues;
 e^{11} is T or I; and
 e^{15}, e^{16} , and e^{17} are each independently absent or amino acid residues;
 f^1, f^2 , and f^3 are absent or are amino acid residues;
15 f^5 is W, Y, or F;
 f^7 is an amino acid residue;
 f^9 is T or I;
 f^{10} is K, R, or H;
 f^{12} is C, a neutral polar residue, or a basic residue;
20 f^{13} is C, a neutral polar residue or is absent; and
 f^{14} is any amino acid residue or is absent;
provided that only one of f^1, f^2 , and f^3 may be C, and only one of f^{12}, f^{13} , and f^{14} may be C;
 g^1, g^2 and g^3 are each independently absent or amino acid residues;
25 g^5 is a neutral polar residue;
 g^8 is a neutral polar residue;
 g^{10} is an acidic residue;
 g^{12} and g^{13} are each independently amino acid residues; and
 g^{14} is absent or is an amino acid residue;
30 h^1, h^2 , and h^3 are each independently absent or amino acid residues;

- h^6 is a hydrophobic residue;
 h^7 is a hydrophobic residue;
 h^{10} is an acidic or polar hydrophobic residue; and
 h^{12} , h^{13} , and h^{14} are each independently absent or amino acid residues;
5 i^1 is absent or is an amino acid residue;
 i^2 is a neutral polar residue;
 i^3 is an amino acid residue;
 i^5 , i^6 , i^7 , and i^8 are each independently amino acid residues;
 i^9 is an acidic residue;
10 i^{10} is an amino acid residue;
 i^{12} and i^{13} are each independently amino acid residues; and
 i^{14} is a neutral polar residue.

38. The composition of matter of claim 37, wherein:

- a^9 is a basic residue.
15 b^3 is D, Q, or E;
 b^6 is W or Y;
 b^{11} is K or R; and
 b^{14} is V or L.
 c^{10} is K or R;
20 c^{13} is a I, L, or V;
 c^{17} is A or L;
 f^5 is W;
 f^7 is L; f^9 is K; and
 f^{10} is V.

- 25 39. The composition of matter of Claim 37, wherein one or more of P^1 , P^2 ,
 P^3 , and P^4 each independently comprises

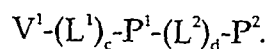
$$f^1 f^2 f^3 K W D f^7 L f^9 K Q f^{12} f^{13} f^{14}$$

(SEQ ID NO: 125).

40. The composition of matter of Claim 39 of the formula

- 30 $P^1-(L^1)_c-P^2-(L^2)_d-V^1$.

41. The composition of matter of Claim 39 of the formula



42. The composition of matter of Claim 39 having an amino acid sequence selected from SEQ ID NOS: 122, 123, and 124.

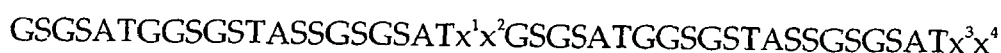
5 43. The composition of matter of Claim 40 wherein L^2 is greater than 5 amino acids.

44. The composition of matter of Claim 43 wherein L^2 is selected from



(SEQ ID NO: 193)

10 and



(SEQ ID NO: 194)

wherein x^1 and x^3 are each independently basic or hydrophobic residues and x^2 and x^4 are each independently hydrophobic residues.

15 45. The composition of matter of Claim 41 wherein L^2 is selected from



(SEQ ID NO: 59),



(SEQ ID NO: 190)

20 $\text{GSGSATGGSGSTASSGSGSATGS}$

(SEQ ID NO: 191), and



(SEQ ID NO: 192).

46. The composition of matter of Claim 28 comprising a sequence selected
25 from Table 2 (SEQ ID NOS: 29-39, 60-70, and 126-188).

47. The composition of matter of Claim 30 comprising a sequence selected from Table 4 (SEQ ID NOS: 44-55).

48. The composition of matter of Claim 46, wherein V^1 is an Fc domain.

49. The composition of matter of Claim 46, wherein V^1 is an IgG Fc
30 domain.

50. The composition of matter of Claim 46, wherein V^l is an IgG1 Fc domain.
51. A DNA encoding a composition of matter of Claim 34.
52. An expression vector comprising the DNA of Claim 51.
53. A host cell comprising the expression vector of Claim 52.
54. The cell of Claim 53, wherein the cell is an *E. coli* cell.
55. A composition of matter as claimed in Claim 1 used in the manufacture of a medicament for treating a B-cell mediated autoimmune disease.
56. A composition of matter as claimed in Claim 13 used in the manufacture of a medicament for treating a B-cell mediated autoimmune disease.
57. A composition of matter as claimed in Claim 1 used in the manufacture of a medicament for treating lupus.
58. A composition of matter as claimed in Claim 13 used in the manufacture of a medicament for treating lupus.
59. A composition of matter as claimed in Claim 1 used in the manufacture of a medicament for treating a B-cell mediated cancer.
60. A composition of matter as claimed in Claim 13 used in the manufacture of a medicament for treating a B-cell mediated cancer.
61. A composition of matter as claimed in Claim 1 used in the manufacture of a medicament for treating a B-cell lymphoma.
62. A composition of matter as claimed in Claim 13 used in the manufacture of a medicament for treating a B-cell mediated lymphoma.

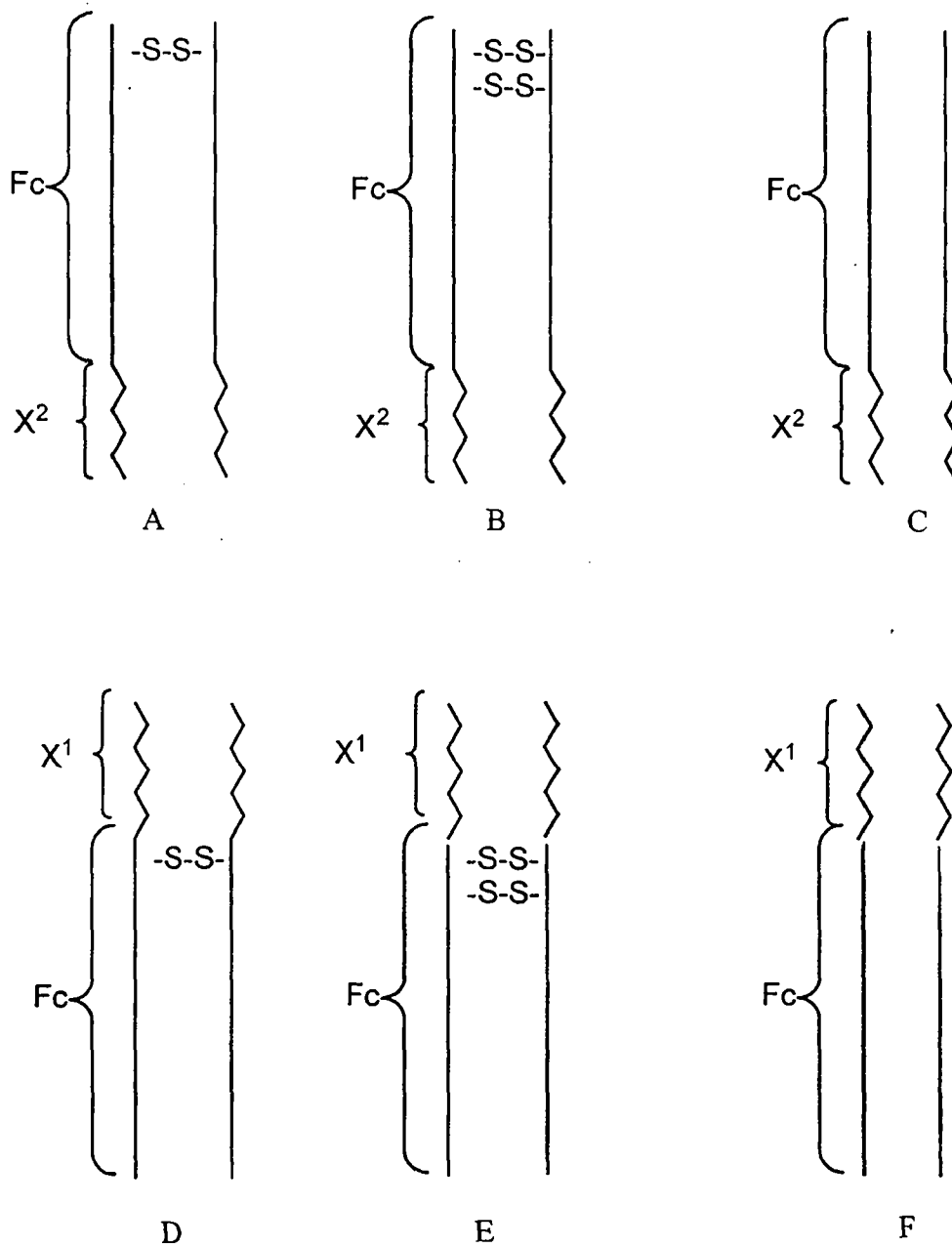
FIG. 1

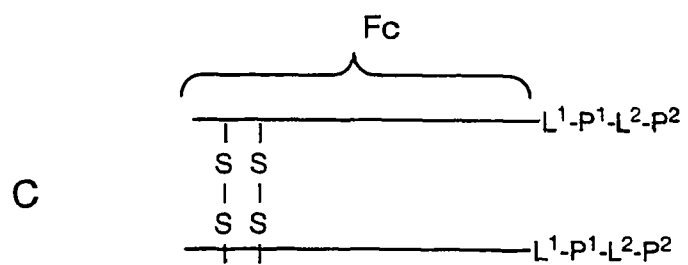
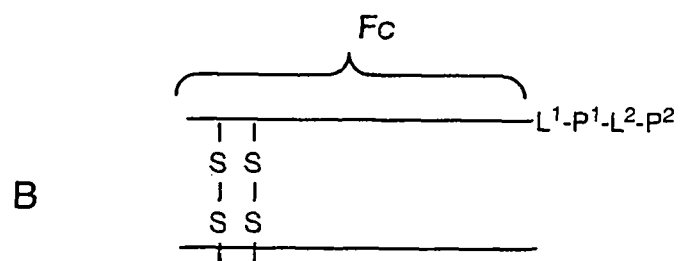
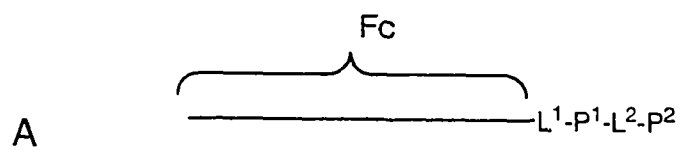
FIG. 2

FIG. 3

```

1  ATGGACAAAACTCACACATGTCCACCTTGTCCAGCTCCGGAACCTCTGGGGGGACCGTCA
   +-----+-----+-----+-----+-----+-----+
61  TACCTGTTTTGAGTGTGTACAGGTGGAACAGGTCGAGGCCTTGAGGACCCCCCTGGCAGT
a   M D K T H T C P P C P A P E L L G G P S -
   +-----+-----+-----+-----+-----+-----+
121 GTCTTCCTCTTCCCCCAAAACCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTC
    +-----+-----+-----+-----+-----+-----+
181 CAGAAGGAGAAGGGGGGTTTTGGGTTCTGTGGGAGTACTAGAGGGCCTGGGGACTCCAG
a   V F L F P P K P K D T L M I S R T P E V -
   +-----+-----+-----+-----+-----+-----+
241 ACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTG
    +-----+-----+-----+-----+-----+-----+
300 TGTACGCACCAACCTGCACTCGGTGCTTCTGGGACTCCAGTTCAAGTTGACCATGCAC
a   T C V V V D V S H E D P E V K F N W Y V -
   +-----+-----+-----+-----+-----+-----+
360 GACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACG
    +-----+-----+-----+-----+-----+-----+
420 CTGCCGCACCTCCACGTATTACGGTCTGTTCGGCGCCCTCCTCGTCATGTTGTCGTGC
a   D G V E V H N A K T K P R E E Q Y N S T -
   +-----+-----+-----+-----+-----+-----+
480 TACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTAC
    +-----+-----+-----+-----+-----+-----+
540 ATGGCACACCAGTCGCAGGAGTGGCAGGACGTGGTCCTGACCGACTTACCGTTCCTCATG
a   Y R V V S V L T V L H Q D W L N G K E Y -
   +-----+-----+-----+-----+-----+-----+
600 AAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAGCC
    +-----+-----+-----+-----+-----+-----+
660 TTCACGTTCAGAGGTTGTTTCGGGAGGGTCGGGGGTAGCTCTTTTGGTAGAGGTTTCGG
a   K C K V S N K A L P A P I E K T I S K A -
   +-----+-----+-----+-----+-----+-----+
720 AAAGGGCAGCCCCGAGAACCACAGGTGTACACCCCTGCCCCCATCCCGGGATGAGCTGACC
    +-----+-----+-----+-----+-----+-----+
780 TTTCCCGTCGGGGCTCTTGGTGTCCACATGTGGGACGGGGGTAGGGCCCTACTCGACTGG
a   K G Q P R E P Q V Y T L P P S R D E L T -
   +-----+-----+-----+-----+-----+-----+
840 AAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTG
    +-----+-----+-----+-----+-----+-----+
900 TTCTTGGTCCAGTCGGAAGTGGACGACAGTTTCCGAAGATAGGGTCGCTGTAGCGGCAC
a   K N Q V S L T C L V K G F Y P S D I A V -
   +-----+-----+-----+-----+-----+-----+
960 GAGTGGGAGAGCAATGGGCAGCCGGAGAACAACCTACAAGACCACGCCTCCCGTGTGGAC
    +-----+-----+-----+-----+-----+-----+
1020 CTCACCCCTCTCGTTACCCGTCGGCCTCTTGTGATGTTCTGGTGGGAGGGCAGGACCTG
a   E W E S N G Q P E N N Y K T T P P V L D -
   +-----+-----+-----+-----+-----+-----+
1080 TCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAG
    +-----+-----+-----+-----+-----+-----+
1140 AGGCTGCCGAGGAAGAAGGAGATGTCGTTGAGTGGCACCTGTTCTCGTCCACCGTCGTC
a   S D G S F F L Y S K L T V D K S R W Q Q -
   +-----+-----+-----+-----+-----+-----+
1200 GGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGAGAAG
    +-----+-----+-----+-----+-----+-----+
1260 CCCTTGAGAAGAGTACGAGGCACTACGTACTCCGAGACGTGTTGGTGTGTCGCTCTTC
a   G N V F S C S V M H E A L H N H Y T Q K -
   +-----+-----+-----+-----+-----+-----+
1320 AGCCTCTCCCTGTCTCCGGGTAAA
    +-----+-----+-----+-----+-----+-----+
1380 TCGGAGAGGGACAGAGGCCCATTT
a   S L S L S P G K

```

FIG. 4A

1) AGP3-8-1-a

NdeI

|

TATGCCGGGTACTTGTTCCTCCGTTCCCGTGGGAATGCACTCACGCTGGTGGAGGCGGT

1 -----+-----+-----+-----+-----+-----+ 60

GGCCCATGAACAAAGGGCAAGGGCACCCCTTACGTGAGTGCGACCACCTCCGCCA

a M P G T C F P F P W E C T H A G G G G -

SalI

|

GGGG

61 ----- 69

CCCCAGCT

a G V D -

2) AGP3-8-2-a

NdeI

|

TATGTGGGGTGCTTGTGGCCGTTCCCGTGGGAATGTTTCAAAGAAGGTGGAGGCGGT

1 -----+-----+-----+-----+-----+-----+ 60

ACACCCACGAACAACCGGCAAGGGCACCCCTTACAAAGTTTCTTCCACCTCCGCCA

a M W G A C W P F P W E C F K E G G G G -

SalI

|

GGGG

61 ----- 69

CCCCAGCT

a G V D -

FIG. 4B

3) AGP3-8-4-a

NdeI
|
TATGGTTCCGTTCTGTGACCTGCTGACTAAACACTGTTTCGAAGCTGGTGGAGGCGGT
1 -----+-----+-----+-----+-----+-----+ 60
ACCAAGGCAAGACACTGGACGACTGATTTGTGACAAAGCTTCGACCACCTCCGCCA
a M V P F C D L L T K H C F E A G G G G -

SalI
|
GGGG
61 ----- 69
CCCCAGCT
a G V D -

4) AGP3-12-4-a

November 6, 2000 12:53 ..

NdeI
|
TATGGGTTCTCGTTGTAAATACAAATGGGACGTTCTGACTAAACAGTGTTCACCAC
1 -----+-----+-----+-----+-----+-----+ 60
ACCCAAGAGCAACATTTATGTTTACCCTGCAAGACTGATTTGTCACAAAGGTGGTG
a M G S R C K Y K W D V L T K Q C F H H -
SalI
|
GGTGGAGGCGGTGGGG
61 -----+-----+----- 81
CCACCTCCGCCACCCAGCT
a G G G G G V D -

FIG. 4C

5) AGP3-12-3-a

NdeI

|

TATGCTGCCGGGTTGTAAATGGGACCTGCTGATCAAACAGTGGGTTTGTGACCCGCTG

1 -----+-----+-----+-----+-----+-----+ 60

ACGACGGCCCAACATTTACCCTGGACGACTAGTTTGTACCCAAACACTGGGCGAC

a M L P G C K W D L L I K Q W V C D P L -

SalI

|

GGTGGAGGCGGTGGGG

61 -----+-----+-----+-----+-----+ 81

CCACCTCCGCCACCCCAGCT

a G G G G G V D -

6) AGP3-12-5-a

NdeI

|

TATGTCTGCTGACTGTTACTTCGACATCCTGACTAAATCTGACGTTTGTACTTCTTCT

1 -----+-----+-----+-----+-----+-----+ 60

ACAGACGACTGACAATGAAGCTGTAGGACTGATTTAGACTGCAAACATGAAGAAGA

a M S A D C Y F D I L T K S D V C T S S -

SalI

|

GGTGGAGGCGGTGGGG

61 -----+-----+-----+-----+-----+ 81

CCACCTCCGCCACCCCAGCT

a G G G G G V D -

FIG. 4D

7) AGP3-12-8-a

NdeI

|

TATGTCTGACGACTGTATGTACGACCAGCTGACTCGTATGTTTCATCTGTTCTAACCTG

1 -----+-----+-----+-----+-----+-----+ 60

ACAGACTGCTGACATACATGCTGGTCGACTGAGCATACAAGTAGACAAGATTGGAC

a M S D D C M Y D Q L T R M F I C S N L -

SalI

|

GGTGGAGGCGGTGGGG

61 -----+-----+-----+-----+-----+ 81

CCACCTCCGCCACCCCAGCT

a G G G G G V D -

8) AGP3-12-9-a

NdeI

|

TATGGACCTGAACTGTAAATACGACGAACTGACTTACAAAGAATGGTGTCAGTTCAAC

1 -----+-----+-----+-----+-----+-----+ 60

ACCTGGACTTGACATTTATGCTGCTTGACTGAATGTTTCTTACCACAGTCAAGTTG

a M D L N C K Y D E L T Y K E W C Q F N -

SalI

|

GGTGGAGGCGGTGGGG

61 -----+-----+-----+-----+-----+ 81

CCACCTCCGCCACCCCAGCT

a G G G G G V D -

FIG. 4E

9) AGP3-12-10-a

NdeI

|

TATGTTCCACGACTGTAAATACGACCTGCTGACTCGTCAGATGGTTTGTCACGGTCTG

1 -----+-----+-----+-----+-----+-----+ 60

ACAAGGTGCTGACATTTATGCTGGACGACTGAGCAGTCTACCAAACAGTGCCAGAC

a M F H D C K Y D L L T R Q M V C H G L -

SalI

|

GGTGGAGGCGGTGGGG

61 -----+-----+----- 81

CCACCTCCGCCACCCCAGCT -

a G G G G G V D -

10) AGP3-12-11-a

NdeI

|

TATGCGTAACCACTGTTTCTGGGACCACCTGCTGAAACAGGACATCTGTCCGTCTCCG

1 -----+-----+-----+-----+-----+ 60

ACGCATTGGTGACAAAGACCCTGGTGGACGACTTTGTCCTGTAGACAGGCAGAGGC

a M R N H C F W D H L L K Q D I C P S P -

SalI

|

GGTGGAGGCGGTGGGG

61 -----+-----+----- 81

CCACCTCCGCCACCCCAGCT

a G G G G G V D -

FIG. 4F

11) AGP3-12-14-a

```
      |
      | NdeI
      | TATGGCTAACCAGTGTTGGTGGGACTCTCTGCTGAAAAAAAAACGTTTGTGAATTCTTC
1  -----+-----+-----+-----+-----+-----+-----+ 60
      | ACCGATTGGTTCACAACCACCCTGAGAGACGACTTTTTTTTGCAAACACTTAAGAAG
a      M A N Q C W W D S L L K K N V C E F F -

      | SalI
      | GGTGGAGGCGGTGGGG
61 -----+-----+-----+-----+-----+-----+ 81
      | CCACCTCCGCCACCCCAGCT
a      G G G G G V D -
```

12) AGP3 Consensus

```
      |
      | NdeI
      | TATGTTCCACGACTGCAAATGGGACCTGCTGACCAAACAGTGGGTTTGCCACGGTCTG
1  -----+-----+-----+-----+-----+-----+ 60
      | gtATACAAGGTGCTGACGTTTACCCTGGACGACTGGTTTGTACCCAAACGGTGCCAGAC
a      M F H D C K W D L L T K Q W V C H G L -

      | SalI
      | GGTGGAGGCGGTGGGG
61 -----+-----+-----+-----+-----+-----+ 81
      | CCACCTCCGCCACCCCAGCT
a      G G G G G V D -
```

P
f
1
1
1
0
8
I

```
GATCAGCAGTCCCCGGAACATCGTAGCTGACGCCTTCGCGTTGCTCAGTTGTCCAACCCC
1  -----+-----+-----+-----+-----+-----+-----+ 60
CTAGTCGTCAAGGGCCTTGTAGCATCGACTGCGGAAGCGCAACGAGTCAACAGGTTGGGG

GGAAACGGGAAAAAGCAAGTTTTCCCCGCTCCCGGCGTTTCAATAACTGAAAACCATACT
61  -----+-----+-----+-----+-----+-----+-----+ 120
CCTTTGCCCTTTTTCGTTCAAAAGGGGCGAGGGCCGCAAAGTTATTGACTTTTGGTATGA

B
g
l
I
I
121  ATTTACAGTTTAAATCACATTAAACGACAGTAATCCCCGTTGATTGTGCGCCAACACA 180
-----+-----+-----+-----+-----+-----+-----+
TAAAGTGTCAAATTTAGTGTAATTTGCTGTCATTAGGGGCAACTAAACACGCGGTTGTGT

-35 -10
-----
-----
----- Promoter (PcopB) ----->
GATCTTCGTCACAATTCTCAAGTCGCTGATTTCAAAAAACTGTAGTATCCTCTGCGAAAC
181  -----+-----+-----+-----+-----+-----+-----+ 240
CTAGAAGCAGTGTTAAGAGTTCAGCGACTAAAGTTTTTTGACATCATAGGAGACGCTTTG
|-->
mRNA start

GATCCCTGTTTGTAGTATTGAGGAGGCGAGATGTGCGAGACAGAAAAATGCAGTGACTTCCT
241  -----+-----+-----+-----+-----+-----+-----+ 300
CTAGGGACAAACTCATAACTCCTCCGCTCTACAGCGTCTGTCTTTTACGTCACTGAAGGA
M S Q T E N A V T S S -
--- copB protein --->

CATTGAGTCAAAAGCGGTTTGTGCGCAGAGGTAAGCCTATGACTGACTCTGAGAAACAAA
301  -----+-----+-----+-----+-----+-----+-----+ 360
GTAAGTCAAGTTTTCGCCAAACACGCGTCTCCATTCCGATACTGACTGAGACTCTTTGTTT
L S Q K R F V R R G K P M T D S E K Q M -

TGGCCGTTGTTGCAAGAAAACGTCTTACACACAAAGAGATAAAAGTTTTTGTCAAAAATC
361  -----+-----+-----+-----+-----+-----+-----+ 420
ACCGGCAACAACGTTCTTTTGCAGAATGTGTGTTTCTCTATTTTCAAAAACAGTTTTTGTAG
A V V A R K R L T H K E I K V F V K N P -

S
c
a
I
421  CTCTGAAGGATCTCATGGTTGAGTACTGCGAGAGAGAGGGGATAACACAGGCTCAGTTTCG 480
-----+-----+-----+-----+-----+-----+-----+
GAGACTTCCTAGAGTACCAACTCATGACGCTCTCTCTCCCTATTGTGTCCGAGTCAAGC
L K D L M V E Y C E R E G I T Q A Q F V -
```

FIG. 5B

```

                                     -35
                                     -----
                                     Promoter (PrepA) ----->
                                     |-- copB binding site --|
481 TTGAGAAAATCATCAAAGATGAACTGCAAAGACTGGATATACTAAAGTAAAGACTTTACT
-----+-----+-----+-----+-----+-----+-----+-----+
541 AACTCTTTTAGTAGTTTCTACTTGACGTTTCTGACCTATATGATTTTCATTTCTGAAATGA
E K I I K D E L Q R L D I L K *

                                     -10
                                     -----
541 TTGTGGCGTAGCATGCTAGATTACTGATCGTTTAAGGAATTTTGTGGCTGGCCACGCCGT
-----+-----+-----+-----+-----+-----+-----+
600 AACACCGCATCGTACGATCTAATGACTAGCAAATTCCTTAAACACCGACCGGTGCGGCA
                                     |-- mRNA -->

                                     D
                                     B r
                                     m d
                                     n i
                                     I I
601 AAGGTGGCAAGGAAGTGGTTCTGATGTGGATTTACAGGAGCCAGAAAAGCAAAAACCCCG
-----+-----+-----+-----+-----+-----+-----+
660 TTCCACCGTTCCTTGACCAAGACTACACCTAAATGTCCTCGGTCTTTTTCGTTTTTGGGGC
M W I Y R S Q K S K N P D -
--- copT (ORF) --->

<----- copA RNAI ----->
661 ATAATCTTCTTCAACTTTTGCGAGTACGAAAAGATTACCGGGGCCCACTTAAACCGTATA
-----+-----+-----+-----+-----+-----+-----+
720 TATTAGAAGAAGTTGAAAACGCTCATGCTTTTCTAATGGCCCCGGGTGAATTTGGCATAT
N L L Q L L R V R K D Y R G P L K P Y S -

<----- Promoter (RNAI) ----->
                                     -10
                                     -----
                                     -35
                                     -----
721 GCCAACAATTCAGCTATGCGGGGAGTATAGTTATATGCCCCGAAAAGTTCAAGACTTCTT
-----+-----+-----+-----+-----+-----+-----+
780 CGGTTGTTAAGTCGATACGCCCCCTCATATCAATATACGGGCCCTTTCAAGTTCTGAAGAA
Q Q F S Y A G S I V I C P E K F K T S F -

781 TCTGTGCTCGCTCCTTCTGCGCATTGTAAGTGCAGGATGGTGTGACTGATCTTCACCAAA
-----+-----+-----+-----+-----+-----+-----+
840 AGACACGAGCGAGGAAGACGCGTAACATTACGTCTTACCACACTGACTAGAAGTGGTTT
C A R S F C A L * M T D L H Q T -
--- repA1 protein --->

                                     D
                                     r
                                     a
                                     i
                                     i
                                     I
841 CGTATTACCGCCAGGTAAAGAACCCGAATCCGGTGTTTACACCCCGTGAAGGTGCAGGAA
-----+-----+-----+-----+-----+-----+-----+
900 GCATAATGGCGGTCCATTTCTTGGGCTTAGGCCACAAATGTGGGGCACTTCCACGTCTT
Y Y R Q V K N P N P V F T P R E G A G T -

901 CGCTGAAGTTCTGCGAAAACTGATGGAAAAGCGGTGGGCTTCACTTCCCGTTTTGATT
-----+-----+-----+-----+-----+-----+-----+
960 GCGACTTCAAGACGCTTTTGTACTACCTTTTCCGCCACCCGAAGTGAAGGGCAAACTAA
L K F C E K L M E K A V G F T S R F D F -

```

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FIG. 5C

B
S
t
B
I

961 TCGCCATTCATGTGGCGCACGCCCCGTTGCGGTGATCTGCGTCGCCGTATGCCACCAAGTGC 1020
 -----+-----+-----+-----+-----+-----+-----+-----+
 AGCGGTAAGTACACCGCGTGCAGGGCAAGCGCACTAGACGCAGCGGCATACGGTGGTCACG
 c A I H V A H A R S R D L R R R M P P V L -

1021 TGCGTCGTGCGGGCTATTGATGCGCTCTTGCGAGGGGCTGTGTTTCCACTATGACCCGCTGG 1080
 -----+-----+-----+-----+-----+-----+-----+-----+
 ACGCAGCAGCCCCGATAACTACGCGAGAACGTCCCCGACACAAAGGTGATACTGGGCGACC
 c R R R A I D A L L Q G L C F H Y D P L A -

1081 CCAACCGCGTCCAGTGCTCCATCACCACGCTGGCCATTGAGTGCGGACTGGCGACGGAGT 1140
 -----+-----+-----+-----+-----+-----+-----+-----+
 GGTTGGCGCAGGTCACGAGGTAGTGGTGCAGCCGGTAACTCACGCCTGACCGCTGCCTCA
 c N R V Q C S I T T L A I E C G L A T E S -

A
C
e
I
I
I

1141 CTGCTGCCGGAAGAACTCTCCATCACCCGTGCCACCCGTGCCCTGACGTTCTGTGTCAGAGC 1200
 -----+-----+-----+-----+-----+-----+-----+-----+
 GACGACGGCCTTTTGAGAGGTAGTGGGCACGGTGGGCACGGGACTGCAAGGACAGTCTCG
 c A A G K L S I T R A T R A L T F L S E L -

1201 TGGGACTGATTACCTACCAGACGGAATATGACCCGCTTATCGGGTGCTACATTCCGACCG 1260
 -----+-----+-----+-----+-----+-----+-----+-----+
 ACCCTGACTAATGGATGGTCTGCCTTATACTGGGCGAATAGCCCACGATGTAAGGCTGGC
 c G L I T Y Q T E Y D P L I G C Y I P T D -

1261 ATATCACGTTTCACATCTGCACTGTTTGCTGCCCTCGATGTATCAGAGGAGGCAGTGGCCG 1320
 -----+-----+-----+-----+-----+-----+-----+-----+
 TATAGTGCAAGTGTAGACGTGACAAACGACGGGAGCTACATAGTCTCCTCCGTACCCGGC
 c I T F T S A L F A A L D V S E E A V A A -

1321 CCGCGCGCCGCGAGCCGTGTGGTATGGGAAAACAAACAACGCAAAAAGCAGGGGCTGGATA 1380
 -----+-----+-----+-----+-----+-----+-----+-----+
 GGCGCGCGGCGTCCGCACACCATAACCTTTTGTGTTGTTGCGTTTTTCGTCCCCGACCTAT
 c A R R S R V V W E N K Q R K K Q G L D T -

1381 CCCTGGGCATGGATGAACTGATAGCGAAAGCCTGGCGTTTTGTTTCGTGAGCGTTTTTCGCA 1440
 -----+-----+-----+-----+-----+-----+-----+-----+
 GGGACCCGTACCTACTTGAATATCGCTTTTCGGACCGCAAAACAAGCACTCGCAAAAGCGT
 c L G M D E L I A K A W R F V R E R F R S -

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1441 GTTATCAGACAGAGCTTAAGTCCCGTGGAATAAAGCGTGCCCGTGCGCGTCGTGATGCGG 1500
 -----+-----+-----+-----+-----+-----+-----+-----+
 CAATAGTCTGTCTCGAATTCAGGGCACCTTATTCGCACGGGCACGCGCAGCACTACGCC
 c Y Q T E L K S R G I K R A R A R R D A D -

FIG. 5D

1501 ACAGGGAACGTCAGGATATTGTCACCCTGGTGAACGGCAGCTGACGCGCGAAATCGCGG 1560
 -----+-----+-----+-----+-----+-----+-----+
 TGTCCCTTGCACTCCTATAACAGTGGGACCACTTTGCCGTCGACTGCGCGCTTTAGCGCC
 c R E R Q D I V T L V K R Q L T R E I A E -
 1561 AAGGGCGCTTCACTGCCAATCGTGAGGCGGTAAACCGCAAGTTGAGCGTCGTGTGAAGG 1620
 -----+-----+-----+-----+-----+-----+-----+
 TTCCCGCGAAGTGACGGTTAGCACTCCGCCATTTTGCGCTTCAACTCGCAGCACACTTCC
 c G R F T A N R E A V K R E V E R R V K E -
 1621 AGCGCATGATTCTGTCACGTAACCGTAATTACAGCCGGCTGGCCACAGCTTCCCCCTGAA 1680
 -----+-----+-----+-----+-----+-----+-----+
 TCGCGTACTAAGACAGTGCATTGGCATTAAATGTCGGCCGACCGGTGTGGAAGGGGGACTT
 c R M I L S R N R N Y S R L A T A S P *
 1681 AGTGACCTCCTCTGAATAATCCGGCCTGCGCCGGAGGCTTCCGCACGTCTGAAGCCCGAC 1740
 -----+-----+-----+-----+-----+-----+-----+
 TCACTGGAGGAGACTTATTAGGCCGGACGCGGCCTCCGAAGGCGTGCAGACTTCGGGCTG
 P
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 M
 I
 1741 AGCGCACAAAAAATCAGCACCATACAAAAACAACCTCATCATCCAGCTTCTGGTGCA 1800
 -----+-----+-----+-----+-----+-----+-----+
 TCGCGTGTTTTTTAGTCGTGGTGTATGTTTTTTGTTGGAGTAGTAGGTCAAGACCACGT
 1801 TCCGGCCCCCCTGTTTTGATACAAAACACGCCTCACAGACGGGGAATTTTGCTTATCC 1860
 -----+-----+-----+-----+-----+-----+-----+
 AGGCCGGGGGGGACAAAAGCTATGTTTTGTGCGGAGTGTCTGCCCTTAAAACGAATAGG
 |----- ori -----
 1861 ACATTAAACTGCAAGGGACTTCCCCATAAGGTTACAACCGTTCATGTCATAAAGCGCCAT 1920
 -----+-----+-----+-----+-----+-----+-----+
 TGTAATTTGACGTTCCCTGAAGGGGTATTCCAATGTTGGCAAGTACAGTATTTTCGCGGTA
 ----- ori -----
 1921 CCGCCAGCGTTACAGGGTGCAATGTATCTTTTAAACACCTGTTTATATCTCCTTTAAACT 1980
 -----+-----+-----+-----+-----+-----+-----+
 GGCGGTGCAATGTCCACGTTACATAGAAAATTTGTGGACAAATATAGAGGAAATTTGA
 ----- | -----
 1981 ACTTAATTACATTCATTTAAAAAGAAAACCTATTCAGTGCCTGTCCTTGGACAGACAGAT 2040
 -----+-----+-----+-----+-----+-----+-----+
 TGAATTAATGTAAGTAAATTTTCTTTTGGATAAGTGACGGACAGGAACCTGTCTGTCTA
 2041 ATGCACCTCCCACCGCAAGCGGGCGGGCCCCCTACCGGAGCCGCTTTAGTTACAACACTCAG 2100
 -----+-----+-----+-----+-----+-----+-----+
 TACGTGGAGGGTGGCGTTCGCCGCCCGGGGATGGCCTCGGCGAAATCAATGTTGTGAGTC
 a M H L P P Q A A G P Y R S R F S Y N T Q -
 --- repA4 protein ---> |----->
 2101 ACACAACCACCAGAAAAACCCCGGTCCAGCGCAGAACTGAAACCACAAAGCCCCTCCCTC 2160
 -----+-----+-----+-----+-----+-----+-----+
 TGTGTTGGTGGTCTTTTTGGGGCCAGGTCGCGTCTTGACTTTGGTGTTCGGGGAGGGAG
 a T Q P P E K P R S S A E L K P Q S P S L -
 2161 ATAAGTGAAGAGCGCCCCGCCCCGGTCCGAAGGGCCGGAACAGAGTCGCTTTTAATTAT 2220
 -----+-----+-----+-----+-----+-----+-----+
 TATTGACTTTTCGCCGGGGCGGGGCCAGGCTTCCCGGCCTTGTCTCAGCGAAAATTAATA
 a I T E K R P R P G P K G R N R V A F N Y -

FIG. 5E

2221 GAATGTTGTAAC TACTTCATCATCGCTGTCAGTCTTCTCGCTGGAAGTTCTCAGTACACG 2280
 -----+-----+-----+-----+-----+-----+-----+
 CTTACAACATTGATGAAGTAGTAGCGACAGTCAGAAGAGCGACCTTCAAGAGTCATGTGC
 a E C C N Y F I I A V S L L A G S S Q Y T -

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 /
 2281 CTCGTAAGCGGCCCTGACGGCCCGCTAACGCGGAGATACGCCCCGACTTCGGGTAAACCC 2340
 -----+-----+-----+-----+-----+-----+-----+
 GAGCATTTCGCCGGGACTGCCGGGCGATTGCGCCTCTATGCGGGGCTGAAGCCCATTG
 a L V S G P D G P L T R R Y A P T S G K P -

 2341 TCGTCGGGACCACTCCGACCGCGCACAGAAGCTCTCTCATGGCTGAAAGCGGGTATGGTC 2400
 -----+-----+-----+-----+-----+-----+-----+
 AGCAGCCCTGGTGAGGCTGGCGCGTGTCTTCGAGAGAGTACCGACTTTCGCCCATACCAG
 a S S G P L R P R T E A L S W L K A G M V -

 2401 TGGCAGGGCTGGGGATGGGTAAGGTGAAATCTATCAATCAGTACCGGCTTACGCCGGGCT 2460
 -----+-----+-----+-----+-----+-----+-----+
 ACCGTCCCCGACCCCTACCCATTCCACTTTAGATAGTTAGTCATGGCCGAATGCGGCCCGA
 a W Q G W G W V R *

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 2461 TCGGCGGTTTTACTCCTGTTTCATATATGAAACAACAGGTCACCGCCTTCCATGCCGCTG 2520
 -----+-----+-----+-----+-----+-----+-----+
 AGCCGCCAAAATGAGGACAAAGTATATACTTTGTTGTCCAGTGGCGGAAGGTACGGCGAC

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 I
 2521 ATGCGGCATATCCTGGTAACGATATCTGAATTGTTATACATGTGTATATACGTGGTAATG 2580
 -----+-----+-----+-----+-----+-----+-----+
 TACGCCGTATAGGACCATTGCTATAGACTTAACAATATGTACACATATATGCACCATTAC

 2581 ACAAAAATAGGACAAGTTAAAAATTTACAGGCGATGCAATGATTCAAACACGTAATCAAT 2640
 -----+-----+-----+-----+-----+-----+-----+
 TGTTTTTATCCTGTTCAATTTTAAATGTCCGCTACGTTACTAAGTTTGTGCATTAGTTA

 2641 ATCGGGGGTGGGCGAAGAACTCCAGCATGAGATCCCCGCGCTGGAGGATCATCCAGCCGG 2700
 -----+-----+-----+-----+-----+-----+-----+
 TAGCCCCCACCCTTCTTGAGGTCGTACTCTAGGGGCGCGACCTCCTAGTAGGTCCGCC

 2701 CGTCCCGGAAAACGATTCCGAAGCCCCAACCTTTTCATAGAAGGCGGCGGTGGAATCGAAAT 2760
 -----+-----+-----+-----+-----+-----+-----+
 GCAGGGCCTTTTGCTAAGGCTTCGGGTGGAAAGTATCTTCCGCCGCCACCTTAGCTTTA

FIG. 5F

[illegible]

FIG. 5G

```

f      A E D Q L E N L V G S L D T K V F L V P -
3481  GCGCCCCCTGCGCTGACAGCCGGAACACGGCGGCATCAGAGCAGCCGATTGTCTGTTGTGC
-----+-----+-----+-----+-----+-----+-----+-----+ 3540
f      CGCGGGGACGCGACTGTCCGCCCTTGTGCCGCCGTAGTCTCGTCGGCTAACAGACAACACG
      R G Q A S L R F V A A D S C G I T Q Q A -
                                     E
                                     a
                                     g
                                     I
3541  CCAGTCATAGCCGAATAGCCTCTCCACCCAAGCGGCCGGAGAACCTGCGTGCAATCCATC
-----+-----+-----+-----+-----+-----+-----+ 3600
f      GGTCAGTATCGGCTTATCGGAGAGGTGGGTTTCGCCGCCCTCTTGGACGCACGTTAGGTAG
      W D Y G F L R E V W A A P S G A H L G D -
3601  TTGTTCAATCATGCGAAACGATCCTCATCCTGTCTCTTGATCTGATCTTGATCCCCCTGCG
-----+-----+-----+-----+-----+-----+-----+ 3660
f      AACAAAGTTAGTACGCTTTGCTAGGAGTAGGACAGAGAACTAGACTAGAACTAGGGGACGC
      Q E I M
<-- APHII (kanamycin resistance) protein --)
                                     -10
                                     <--- mRNA APHII ---|
3661  CCATCAGATCCTTGGCGGCAAGAAAGCCATCCAGTTTACTTTGCAGGGCTTCCCAACCTT
-----+-----+-----+-----+-----+-----+-----+ 3720
      GGTAGTCTAGGAACCGCCGTTCTTTTCGGTAGGTCAAATGAAACGTCCCGAAGGGTTGGAA

                                     -35
                                     -----
<----- Promoter (APHII) -----
3721  ACCAGAGGGGCGCCCCAGCTGGCAATTCCGGTTCGCTTGCTGTCCATAAAACCGCCAGTC
-----+-----+-----+-----+-----+-----+-----+ 3780
      TGGTCTCCCCGCGGGGTCGACCGTTAAGGCCAAGCGAACGACAGGTATTTTGGCGGGTCAG

      TAGCTATCGCCATGTAAGCCCACTGCAAGCTACCTGCTTTCTCTTTGCGCTTGCGTTTTC
3781  -----+-----+-----+-----+-----+-----+ 3840
      ATCGATAGCGGTACATTTCGGGTGACGTTTCGATGGACGAAAGAGAAACGCGAACGCAAAAG

      CCTTGTCAGATAGCCCAGTAGCTGACATTCATCCGGGGTCAGCACCGTTTCTGCGGACT
3841  -----+-----+-----+-----+-----+-----+-----+ 3900
      GGAACAGGTCTATCGGGTCATCGACTGTAAGTAGGCCCCAGTCGTGGCAAAGACGCCTGA

      GGCTTTCTACGTGTTCCGCTTCCTTTAGCAGCCCTTGCGCCCTGAGTGCCTTGCGGCAGCG
3901  -----+-----+-----+-----+-----+-----+-----+ 3960
      CCGAAAGATGCACAAGGCGAAGGAAATCGTCGGGAACGCGGGACTCACGAACGCCGTCGC

      |----- par locus -----
3961  TGAAGCTACATATATGTGATCCGGGCAAATCGCTGAATATTCCTTTTGTCTCCGACCATC
-----+-----+-----+-----+-----+-----+-----+ 4020
      ACTTCGATGTATATACACTAGGCCCGTTTAGCGACTTATAAGGAAAACAGAGGCTGGTAG

                                     B
                                     c
                                     g
                                     I
      ----- par locus -----
4021  AGGCACCTGAGTCGCTGTCTTTTTCGTGACATTCAGTTCGCTGCGCTCACGGCTCTGGCA
-----+-----+-----+-----+-----+-----+-----+ 4080
      TCCGTGGACTCAGCGACAGAAAAAGCACTGTAAGTCAAGCGACGCGAGTGCCGAGACCGT

      ----- par locus -----

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FIG. 5H

```
GTGAATGGGGGTAAATGGCACTACAGGCGCCTTTTATGGATTCATGCAAGGAACTACCC
4081 -----+-----+-----+-----+-----+-----+-----+ 4140
CACTTACCCCCATTTACCGTGATGTCCGCGGAAAAATACCTAAGTACGTTCTTTGATGGG

----- par locus -----
ATAATACAAGAAAAGCCCGTCACGGGCTTCTCAGGGCGTTTTATGGCGGGTCTGCTATGT
4141 -----+-----+-----+-----+-----+-----+-----+ 4200
TATTATGTTCTTTTCGGGCAGTGCCCCGAAGAGTCCCGCAAAATACCGCCCAGACGATACA

----- par locus -----
GGTGCTATCTGACTTTTTGCTGTTTCAGCAGTTCCTGCCCTCTGATTTTCCAGTCTGACCA
4201 -----+-----+-----+-----+-----+-----+-----+ 4260
CCACGATAGACTGAAAAACGACAAGTCGTCAAGGACGGGAGACTAAAAGGTCAGACTGGT

----- par locus -----
CTTCGGATTATCCCGTGACAGGTCATTACAGCTGGCTAATGCACCCAGTAAGGCAGCGGT
4261 -----+-----+-----+-----+-----+-----+-----+ 4320
GAAGCCTAATAGGGCACTGTCCAGTAAGTCTGACCGATTACGTGGGTCAATCCGTCGCCA

                                     N      B
                                     s      s
                                     i      a
                                     I      I
-----|-----
ATCATCAACAGGCTTACCCGTCTTACTGTCTGAAGACGTGCGTAACGTATGCATGGTCTCC
4321 -----+-----+-----+-----+-----+-----+-----+ 4380
TAGTAGTTGTCCGAATGGGCAGAATGACAGCTTCTGCACGCATTGCATACGTACCAGAGG

                                     T1 hairpin
                                     ----->-----<-----
CCATGCGAGAGTAGGGAAGTCCAGGCATCAAATAAAACGAAAGGCTCAGTCGAAAGACT
4381 -----+-----+-----+-----+-----+-----+-----+ 4440
GGTACGCTCTCATCCCTTGACGGTCCGTAGTTTATTTTGCTTTCCGAGTCAGCTTTCTGA

-----|-----
GGGCCTTTTCGTTTTATCTGTTGTTTGTCTGGTGAACGCTCTCCTGAGTAGGACAAATCCGC
4441 -----+-----+-----+-----+-----+-----+-----+ 4500
CCCGGAAAGCAAAATAGACAACAAACAGCCACTTGCGAGAGGACTCATCCTGTTTAGGCG
-- T1 stop -->|

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CGGGAGCGGATTTGAACGTTGCGAAGCAACGGCCCCGAGGGTGGCGGGCAGGACGCCCCG
4501 -----+-----+-----+-----+-----+-----+-----+ 4560
GCCCTCGCCTAAACTTGCAACGCTTCGTTGCCGGGCTCCACCGCCCGTCTGCGGGCG

                                     T2 hairpin
                                     ----->-----<-----
CATAAACTGCCAGGCATCAAATTAAGCAGAAGGCCATCCTGACGGATGGCCTTTTTGCGT
4561 -----+-----+-----+-----+-----+-----+-----+ 4620
GTATTTGACGGTCCGTAGTTAATTCGTCTTCCGGTAGGACTGCCTACCGGAAAAACGCA
----- T2 stop ----->|
```

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4621 TTCTACAAACTCTTTTGTTTATTTTCTAAATACATTCAAATATGGACGTCGTACTTAAC 4680
 -----+-----+-----+-----+-----+
 AAGATGTTTGAGAAAACAAATAAAAAGATTTATGTAAGTTTATACCTGCAGCATGAATTG
 * -

4681 TTTTAAAGTATGGGCAATCAATTGCTCCTGTTAAAATTGCTTTAGAAATACTTTGGCAGC 4740
 -----+-----+-----+-----+-----+
 AAAATTTTCATACCCGTTAGTTAACGAGGACAATTTTAACGAAATCTTTATGAAACCGTCG
 d * S K F Y P C D I A G T L I A K S I S Q C -
 |<--- luxR protein ---

4741 GGTTTGTTGTATTGAGTTTCATTTGCGCATTGGTTAAATGGAAAGTGACCGTGCGCTTAC 4800
 -----+-----+-----+-----+-----+
 CCAAACAACATAACTCAAAGTAAACGCGTAACCAATTTACCTTTCACTGGCACGCGAATG
 d R N T T N L K M Q A N T L H F T V T R K -

4801 TACAGCCTAATATTTTTGAAATATCCCAAGAGCTTTTTCCTTCGCATGCCACGCTAAAC 4860
 -----+-----+-----+-----+-----+
 ATGTCGGATTATAAAAACTTTATAGGGTTCTCGAAAAAGGAAGCGTACGGGTGCGATTG
 d S C G L I K S I D W S S K G E C A W A L -

4861 ATTCTTTTTCTCTTTTGGTTAAATCGTTGTTTGATTATTATTGCTATATTTATTTTTC 4920
 -----+-----+-----+-----+-----+
 TAAGAAAAAGAGAAAACCAATTTAGCAACAACTAAATAATAAACGATATAAATAAAAAAG
 d C E K E R K T L D N N S K N N A I N I K -

4921 GATAATTATCAACTAGAGAAGGAACAATTAATGGTATGTTTCATACACGCATGTAAAAATA 4980
 -----+-----+-----+-----+-----+
 CTATTAATAGTTGATCTCTTCCTTGTTAATTACCATAACAAGTATGTGCGTACATTTTAT
 d R Y N D V L S P V I L P I N M C A H L F -

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4981 AACTATCTATATAGTTGTCTTTCTCTGAATGTGCAAACTAAGCATTCCGAAGCCATTAT 5040
 -----+-----+-----+-----+-----+
 TTGATAGATATATCAACAGAAAGAGACTTACACGTTTGGATTGTAAGGCTTCGGTAATA
 d L S D I Y N D K E S H A F S L M G F G N -

5041 TAGCAGTATGAATAGGGAACTAAACCCAGTGATAAGACCTGATGATTTGCTTCTTTAA 5100
 -----+-----+-----+-----+-----+
 ATCGTCATACTTATCCCTTTGATTTGGGTCACTATTCTGGACTACTAAAGCGAAGAAATT
 d N A T H I P F S F G T I L G S S K A E K -

5101 TTACATTTGGAGATTTTTTATTTACAGCATTGTTTTCAAATATATTCCAATTAATCGGTG 5160
 -----+-----+-----+-----+-----+
 AATGTAAACCTCTAAAAAATAAATGTCGTAACAAAAGTTTATATAAGGTTAATTAGCCAC
 d I V N P S K K N V A N N E F I N W N I P -

5161 AATGATTGGAGTTAGAATAATCTACTATAGGATCATATTTTATTAAATTAGCGTCATCAT 5220
 -----+-----+-----+-----+-----+
 TTAATAACCTCAATCTTATTAGATGATATCCTAGTATAAAATAATTTAATCGCAGTAGTA
 d S H N S N S Y D V I P D Y K I L N A D D -

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FIG. 5J

5221 AATATTGCCTCCATTTTTTTAGGGTAATTATCCAGAATTGAAATATCAGATTTAACCATAG 5280
 -----+-----+-----+-----+-----+-----+
 TTATAACGGAGGTAAAAAATCCCATTAATAGGTCTTAACCTTTATAGTCTAAATTGGGTATC
 Y Y Q R W K K P Y N D L I S I D S K V M -
 d
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 I
 5281 AATGAGGATAAATGATCGCGAGTAAATAATATTCACAATGTACCATTTTAGTCATATCAG 5340
 -----+-----+-----+-----+-----+-----+
 TTACTCCTATTTACTAGCGCTCATTATTATAAGTGTTACATGGTAAATCAGTATAGTC
 S H P Y I I A L L Y Y E C H V M K T M D -
 5341 ATAAGCATTGATTAATATCATTATTGCTTCTACAGGCTTTAATTTTATTAATTATTCTGT 5400
 -----+-----+-----+-----+-----+-----+
 TATTCGTAACATAATTATAGTAATAACGAAGATGTCCGAAATTAAAATAATTAATAAGACA
 S L C Q N I D N N S R C A K I K N I I R -
 5401 AAGTGTCGTCGGCATTTATGTCTTTCATACCCATCTCTTTATCCTTACCTATTGTTTGTC 5460
 -----+-----+-----+-----+-----+-----+
 TTCACAGCAGCCGTAAATACAGAAAGTATGGGTAGAGAAATAGGAATGGATAACAAACAG
 Y T D D A N I D K M
 <---- luxR protein ---|
 GCAAGTTTTGCGTGTTATATATCATTAAAACGGTAATAGATTGACATTTGATTCTAATAA
 5461 -----+-----+-----+-----+-----+-----+ 5520
 CGTTCAAACGCACAATATATAGTAATTTTGCCATTATCTAACTGTAAACTAAGATTATT
 <-----| <-----| <-----| <----- Promoter (luxPL) -----
 luxR mRNA start sites
 CRP Binding Site

 ATTGGATTTTTGTACACTATTATATCGCTTGAAATACAATTGTTTAAACATAAGTACCTG
 5521 -----+-----+-----+-----+-----+-----+ 5580
 TAACCTAAAAACAGTGTGATAATATAGCGAACTTTATGTTAACAAATTGTATTCATGGAC
 -----+-----+-----+-----+-----+-----+
 lux operator site -35 -10 C B
 -----+-----+-----+-----+-----+-----+ 1 b
 TAGGATCGTACAGGTTTACGCAAGAAATGGTTTGTATAGTCGATTAATCGATTGATT I a
 5581 -----+-----+-----+-----+-----+-----+ 5640
 ATCCTAGCATGTCCAAATGCGTTCTTTTACCAACAATATCAGCTAATTAGCTAAACTAA
 |---- 1209-85 -----> |-- mRNA start -->
 NdeI
 |
 5641 CTAGATTTGTTTTAACTAATTAAAGGAGGAATAACATATGATCGCTCCACCATGCACCAG 5700
 -----+-----+-----+-----+-----+-----+
 GATCTAAACAAAATTGATTAATTTCTCCTTATTGTATACTAGCGAGGTGGTACGTGGTC
 b M I A P P C T S -
 |-- RANK -->
 5701 TGAGAAGCATTATGAGCATCTGGGACGGTGCTGTAACAAAATGTGAACCAGGAAAGTACAT 5760
 -----+-----+-----+-----+-----+-----+
 ACTCTTCGTAATACTCGTAGACCCTGCCACGACATTGTTTACACTTGGTCCTTTCATGTA
 b E K H Y E H L G R C C N K C E P G K Y M -

FIG. 5K

5761 GTCTTCTAAATGCACTACTACCTCTGACAGTGTATGTCTGCCCTGTGGCCCGGATGAATA 5820
-----+-----+-----+-----+
CAGAAGATTTACGTGATGATGGAGACTGTCACATACAGACGGGACACCGGGCCTACTTAT

b S S K C T T T S D S V C L P C G P D E Y -

5821 CTTGGATAGCTGGAATGAAGAAGATAAAATGCTTGCTGCATAAAGTTTGTGATACAGGCAA 5880
-----+-----+-----+-----+
GAACCTATCGACCTTACTTCTTCTATTTACGAACGACGTATTTCAAACACTATGTCCGTT

b L D S W N E E D K C L L H K V C D T G K -

5881 GGCCCTGGTGGCCGTGGTCCGCCGCAACAGTACGACCCCCCGGCGCTGCGCGTGCACGGC 5940
-----+-----+-----+-----+
CCGGGACCACCGGCACCAGCGGCCGTTGTCATGCTGGGGGGCCGCGACGCGCACGTGCCG

b A L V A V V A G N S T T P R R C A C T A -

5941 TGGGTACCACTGGAGCCAGGACTGCGAGTGTGCTGCCGCCGCAACACCGAGTGC GCGCCGGG 6000
-----+-----+-----+-----+
ACCCATGGTGACCTCGGTCTCTGACGCTCACGACGGCGGCGTTGTGGCTCACGCGGGCCC

b G Y H W S Q D C E C C R R N T E C A P G -

6001 CCTGGGCGCCCAGCACCCGTTGCAGCTCAACAAGGACACAGTGTGCAAACCTTGCCTTGC 6060
-----+-----+-----+-----+
GGACCCGCGGGTCTGTGGGCAACGTCGAGTTGTTCTCTGTGTACACGTTTGAACGGAACG

b L G A Q H P L Q L N K D T V C K P C L A -

6061 AGGCTACTTCTCTGATGCCTTTTCTCCACGGACAAATGCAGACCCTGGACCAACTGTAC 6120
-----+-----+-----+-----+
TCCGATGAAGAGACTACGAAAAGGAGGTGCCTGTTTACGTCTGGGACCTGGTTGACATG

b G Y F S D A F S S T D K C R P W T N C T -

6121 CTTCTTGGAAAGAGAGTAGAACATCATGGGACAGAGAAATCCGATGTGGTTTGCAGTTC 6180
-----+-----+-----+-----+
GAAGGAACCTTTCTCTCATCTTGTAGTACCCTGTCTCTTTAGGCTACACCAAACGTCAAG

b F L G K R V E H H G T E K S D V V C S S -

6181 TTCTCTGCCAGCTAGAAAACCACCAAATGAACCCCATGTTTACGTGACAAAACCTCACAC 6240
-----+-----+-----+-----+
AAGAGACGGTCGATCTTTTGGTGGTTTACTTGGGGTACAAATGCAGCTGTTTTGAGTGTG

b S L P A R K P P N E P H V Y V D K T H T -
<-- end RANK --||--start Fc-->

FIG. 5M

b

Q P E N N Y K T T P P V L D S D G S F F -

6781 CCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATG 6840
-----+-----+-----+-----+-----+-----+-----+
GGAGATGTCGTTTCGAGTGGCACCTGTTCTCGTCCACCGTCGTCCCCTTGAGAAGAGTAC

b

L Y S K L T V D K S R W Q Q G N V F S C -

6841 CTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCC 6900
-----+-----+-----+-----+-----+-----+-----+
GAGGCACTACGTACTCCGAGACGTGTTGGTGATGTGCGTCTTCTCGGAGAGGGACAGAGG

b

S V M H E A L H N H Y T Q K S L S L S P -

BamHI
|

6901 GGGTAAATAATGGATCCGCGGAAAGAAGAAGAAGAAGAAGAGCCCGAAAGGAAGCTGA 6960
-----+-----+-----+-----+-----+-----+-----+
CCCATTTATTACCTAGGCGCCTTTCTTCTTCTTCTTCTTCTTCGGGCTTTCCTTCGACT

b

G K *

BlpI
|

T7 hairpin
-----> <---

6961 GTTGGCTGCTGCCACCGCTGAGCAATAACTAGCATAACCCCTTGGGGCCTCTAAACGGGT 7020
-----+-----+-----+-----+-----+-----+-----+
CAACCGACGACGGTGGCGACTCGTTATTGATCGTATTGGGGAACCCCGGAGATTGCCCCA
----->

<-----
7021 CTTGAGGGGTTTTTTTGCTGAAAGGAGGAACCGCTCTTCACGCTCTTCACGCGGATAAATA 7080
-----+-----+-----+-----+-----+-----+-----+
GAACTCCCCAAAAAACGACTTTCTCCTTGCGGAGAAGTGCGAGAAGTGCGCCTATTTAT
-T7 stop ---->|

toop hairpin
----->

7081 AGTAACGATCCGGTCCAGTAATGACCTCAGAACTCCATCTGGATTGTTCAGAACGCTCG 7140
-----+-----+-----+-----+-----+-----+-----+
TCATTGCTAGGCCAGGTCATTACTGGAGTCTTGAGGTAGACCTAAACAAGTCTTGCGAGC

toop hairpin
<-----

7141 GTTGCCGCGCGGGCGTTTTTTATTGGTGAGAATCGCAGCAACTTGTGCGGCCAATCGAGCC 7200
-----+-----+-----+-----+-----+-----+-----+
CAACGGCGGCGCCGCAAAAAATAACCACTCTTAGCGTCGTTGAACAGCGCGGTTAGCTCGG
-- toop stop -->|

7201 ATGTCGTCGTCAACGACCCCCCATTCAAGAACAGCAAGCAGCATTGAGAACCTTGGAAATC 7260
-----+-----+-----+-----+-----+-----+-----+
TACAGCAGCAGTTGCTGGGGGGTAAGTTCTTGTCGTTCTGTCGTAACCTCTTGAAACCTTAG

7261 CAGTCCCTCTTCCACCTGCTGACCG 7285
-----+-----+-----+-----+-----+
GTCAGGGGAGAAGGTGGACGACTGGC

FIG. 6A

[AatII sticky end] (position #4358 in pAMG31) 5' GCGTAACGTATGCATGGTCTCC-
3' TGCACGCATTGCATACGTACCAGAGG-

-CCATGCGAGAGTAGGGAACGCCAGGCATCAAATAAAACGAAAGGCTCAGTCGAAAGACT-
-GGTACGCTCTCATCCCTTGACGGTCCGTAGTTTATTTTGCTTCCGAGTCAGCTTTCTGA-
-GGGCCTTTCGTTTATCTGTTGTTGTGCGGTGAACGCTCTCCTGAGTAGGACAAATCCGC-
-CCCGGAAAGCAAAATAGACAACAAACAGCCACTTGCGAGAGGACTCATCTGTTTAGGCG-
-CGGGAGCGGATTTGAACGTTGCGAAGCAACGGCCCGGAGGGTGGCGGGCAGGACGCCCGC-
-GCCCTCGCTAAACTTGCAACGCTTCGTTGCCGGGCCTCCACCGCCCGTCTGCGGGCG-
-CATAAATGCCAGGCATCAAATTAAGCAGAAGGCCATCCTGACGGATGGCCTTTTTCGCT-
-GTATTTGACGGTCCGTAGTTTAAATTCGCTCTCCGGTAGGACTGCCTACCGGAAAAACGCA-

AatII

-TTCTACAACTCTTTTGTATTTTCTAAATACATTCAAATATGGACGTCGTACTTAAC-
-AAGATGTTTGAGAAAAACAAATAAAAGATTTATGTAAGTTTATACCTGCAGCATGAATTG-
-TTTTAAAGTATGGGCAATCAATTGCTCCTGTAAAATTGCTTTAGAAATACTTTGGCAGC-
-AAAATTTTCATACCCGTTAGTTAACGAGGACAATTTAACGAAATCTTTATGAAACCGTCG-
-GGTTTGTGTATTGAGTTTCATTTGCGCATTTGGTTAAATGGAAAGTGACCGTGCGCTTAC-
-CCAAACAACATAACTCAAAGTAAACGCGTAACCAATTTACCTTCACTGGCACGCGAATG-
-TACAGCCTAATATTTTGAATATCCCAAGAGCTTTTTCCTTCGCATGCCACGCTAAAC-
-ATGTCGGATTATAAAACTTTATAGGGTTCTCGAAAAAGGAAGCGTACGGGTGCGATTG-
-ATTCTTTTCTCTTTTGGTTAAATCGTTGTTGATTATTTATTTGCTATATTTATTTTTC-
-TAAGAAAAAGAGAAAAACCAATTTAGCAACAACTAAATAATAACGATATAAATAAAAG-
-GATAATTATCAACTAGAGAAGGAACAATTAATGGTATGTTTCATACACGCATGTAAAAATA-
-CTATTAATAGTTGATCTCTTCCTTGTTAATTACCATAACAAGTATGTGCGTACATTTTAT-
-AACTATCTATATAGTTGTCTTCTCTGAATGTGCAAACTAAGCATTCCGAAGCCATTAT-
-TTGATAGATATATCAACAGAAAGAGACTTACACGTTTTGATTGTAAGGCTTCGGTAATA-
-TAGCAGTATGAATAGGGAACTAAACCCAGTGATAAGACCTGATGATTTTCGCTTCTTTAA-
-ATCGTCATACTTATCCCTTTGATTTGGGTCACTATTCTGGACTACTAAAGCGAAGAAATT-
-TTACATTTGGAGATTTTTTATTTACAGCATTGTTTTCAAATATATTCCAATTAATCGGTG-
-AATGTAAACCTCTAAAAAATAAATGTCGTAACAAAAGTTTATATAAGGTTAATTAGCCAC-
-AATGATTGGAGTTAGAATAATCTACTATAGGATCATATTTTATTAAATTAGCGTCATCAT-
-TTACTAACCTCAATCTTATTAGATGATATCCTAGTATAAAATAATTTAATCGCAGTAGTA-
-AATATTGCCTCCATTTTTTAGGGTAATTATCCAGAATTGAAATATCAGATTTAACCATAG-
-TTATAACGGAGGTAAAAAATCCCATTAATAGGTCTTAACTTTATAGTCTAAATTGGTATC-
-AATGAGGATAAATGATCGCGAGTAAATAATTCACAATGTACCATTTTAGTCATATCAG-
-TTACTCCTATTTACTAGCGCTCATTTATTATAAGTGTTACATGGTAAAAATCAGTATAGTC-
-ATAAGCATTGATTAATATCATTATTGCTTCTACAGGCTTTAATTTTATTAATTATTCTGT-
-TATTCGTAACCTAATTATAGTAATAACGAAGATGTCGAAATTAAAAATAATTAATAAGACA-
-AAGTGTCGTCGGCATTATGTCTTTCATACCCATCTCTTTATCCTTACCTATTGTTTGTC-
-TTCACAGCAGCCGTAAATACAGAAAGTATGGGTAGAGAAATAGGAATGGATAACAAACAG-
-GCAAGTTTTCGCTGTTATATATCATTTAAACGGTAATAGATTGACATTTGATTCTAATAA-
-CGTTCAAACGCACAATATATAGTAATTTTGCCATTATCTAACTGTAACTAAGATTATT-

FIG. 6B

-ATTGGATTTTTGTCACACTATTATATCGCTTGAAATACAATTGTTTAACATAAGTACCTG-
-TAACCTAAAAACAGTGTGATAATATAGCGAACTTTATGTAAACAAATTGTATTCATGGAC-
-TAGGATCGTACAGGTTTACGCAAGAAAATGGTTTGTATAGTCGATTAATCGATTTGATT-
-ATCCTAGCATGTCCAAATGCGTTCCTTTACCAAACAATATCAGCTAATTAGCTAAACTAA-
-CTAGATTTGTTTTAACTAATTAAAGGAGGAATAACATATGGTTAACGCGTTGGAATTCGA-
-GATCTAAACAAAATTGATTAATTTCTCCTTATTGTATACCAATTGCGCAACCTTAAGCT-
-GCTCACTAGTGTGACCTGCAGGGTACCATGGAAGCTTACTCGAGGATCCGCGGAAAGAA-
-CGAGTGATCACAGCTGGACGTCCCATGGTACCTTCGAATGAGCTCCTAGGCGCCTTTCTT-
-GAAGAAGAAGAAGAAAGCCCGAAAGGAAGCTGAGTTGGCTGCTGCCACCGCTGAGCAATA-
-CTTCTTCTTCTTCTTTCGGGCTTTCCTTCGACTCAACCGACGACGGTGGCGACTCGTTAT-
-ACTAGCATAACCCCTTGGGGCCTCTAAACGGGTCTTGAGGGGTTTTTTTGCTGAAAGGAGG-
-TGATCGTATTGGGGAACCCCGAGATTTGCCCAGAACTCCCCAAAAAACGACTTTCCTCC-
-AACCGCTCTTCACGCTCTTCACGC 3' [SacII sticky end]
-TTGGCGAGAAGTGCGAGAAGTG 5' (position #5904 in pAMG21)

FIG. 7

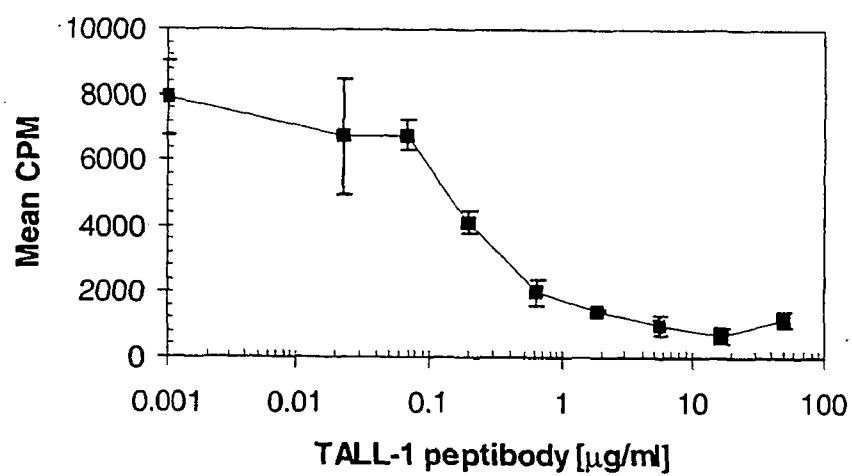


FIG. 8

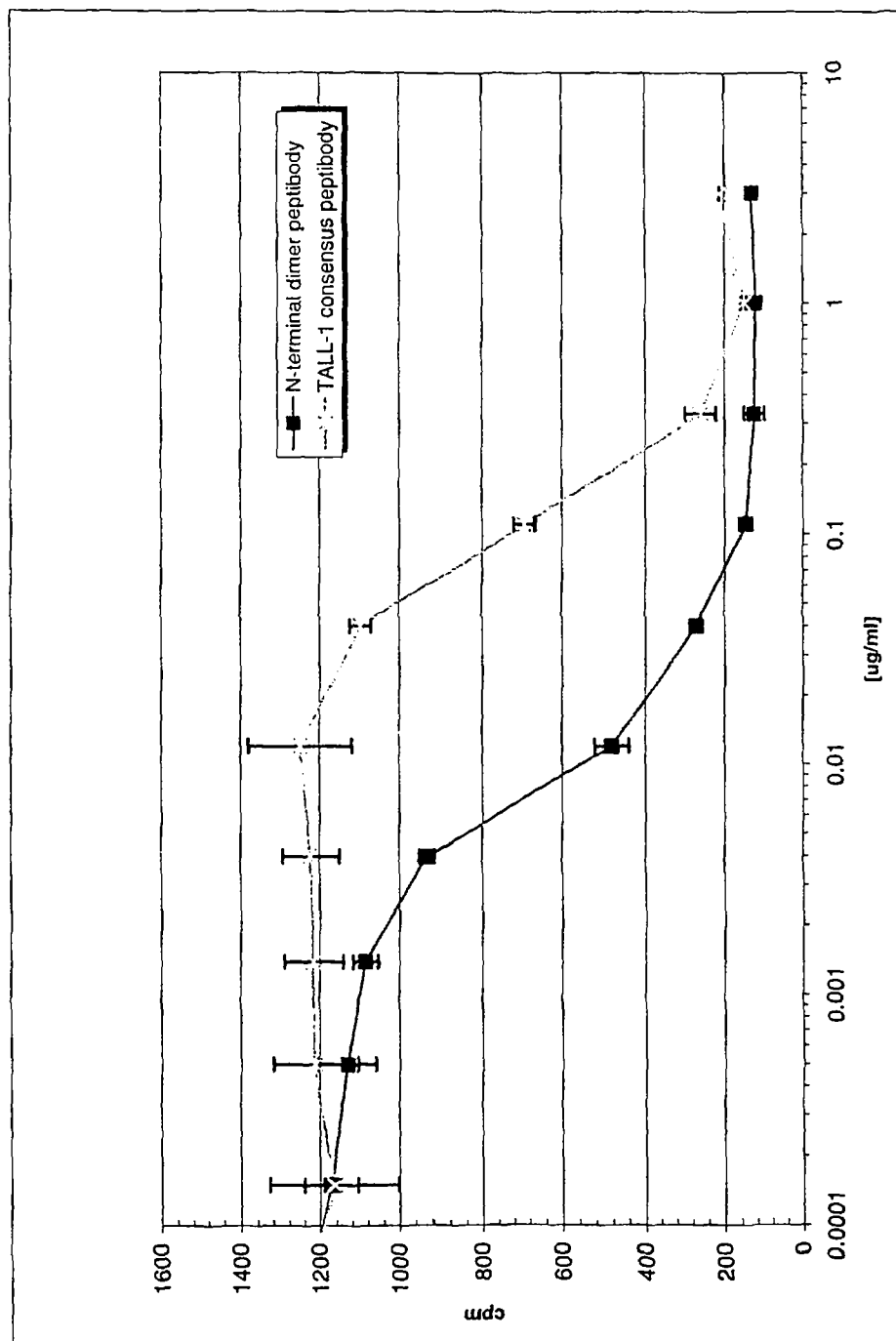


FIG. 9

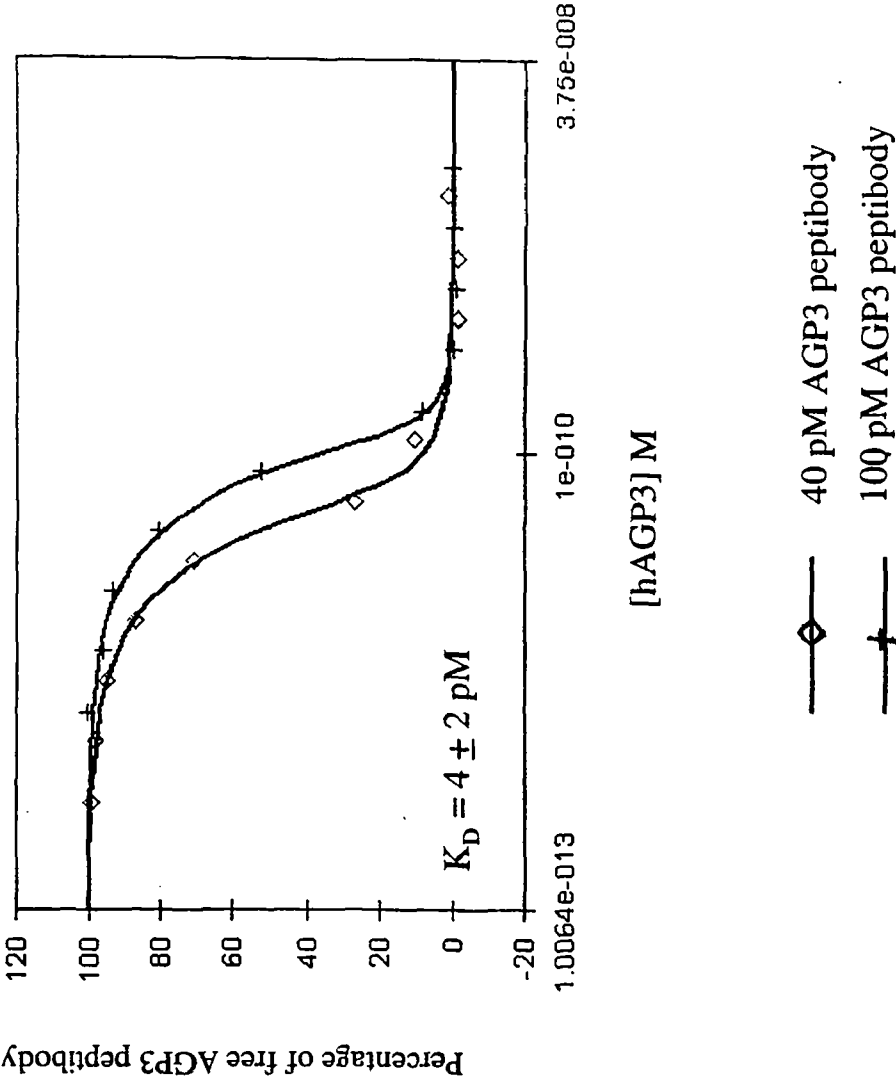


FIG. 10A

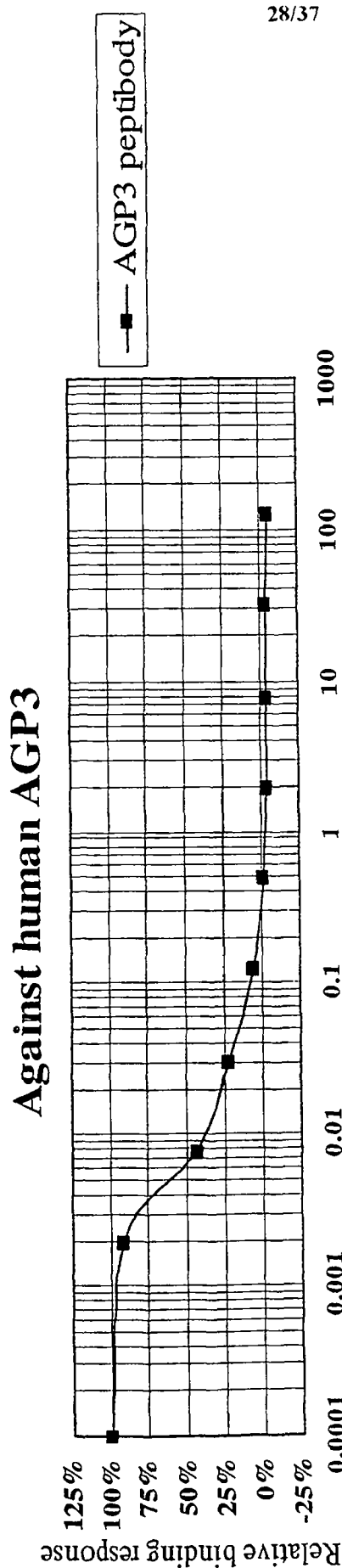


FIG. 10B

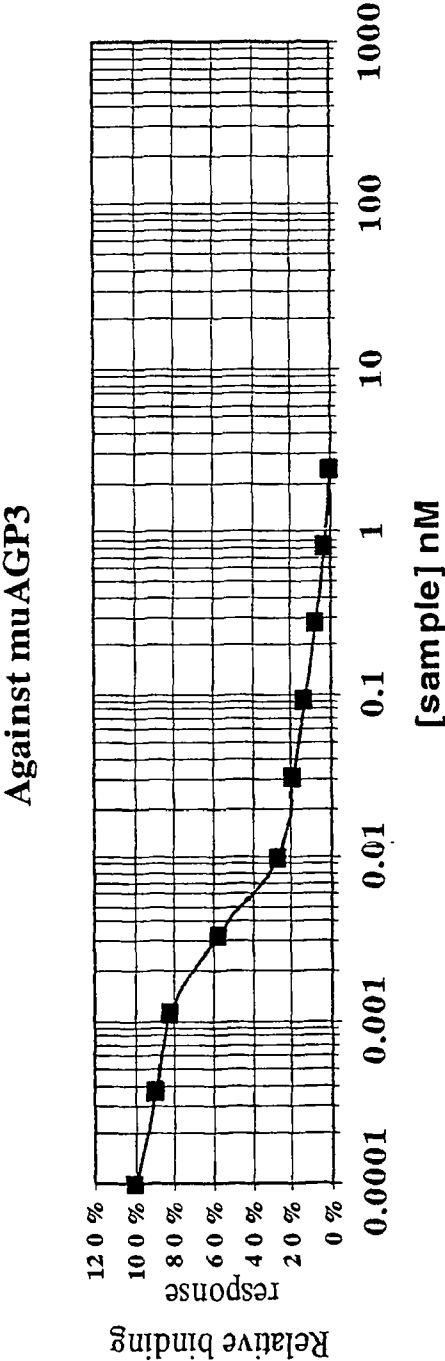


FIG. 11A

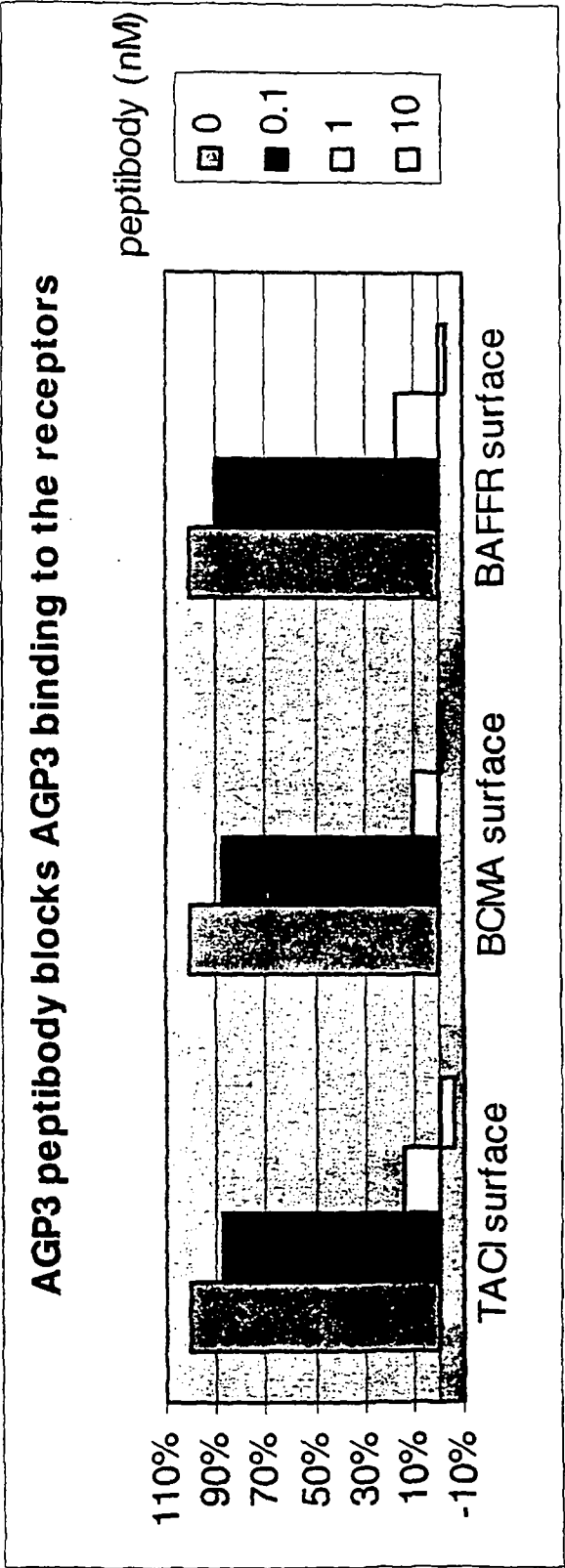


FIG. 11B

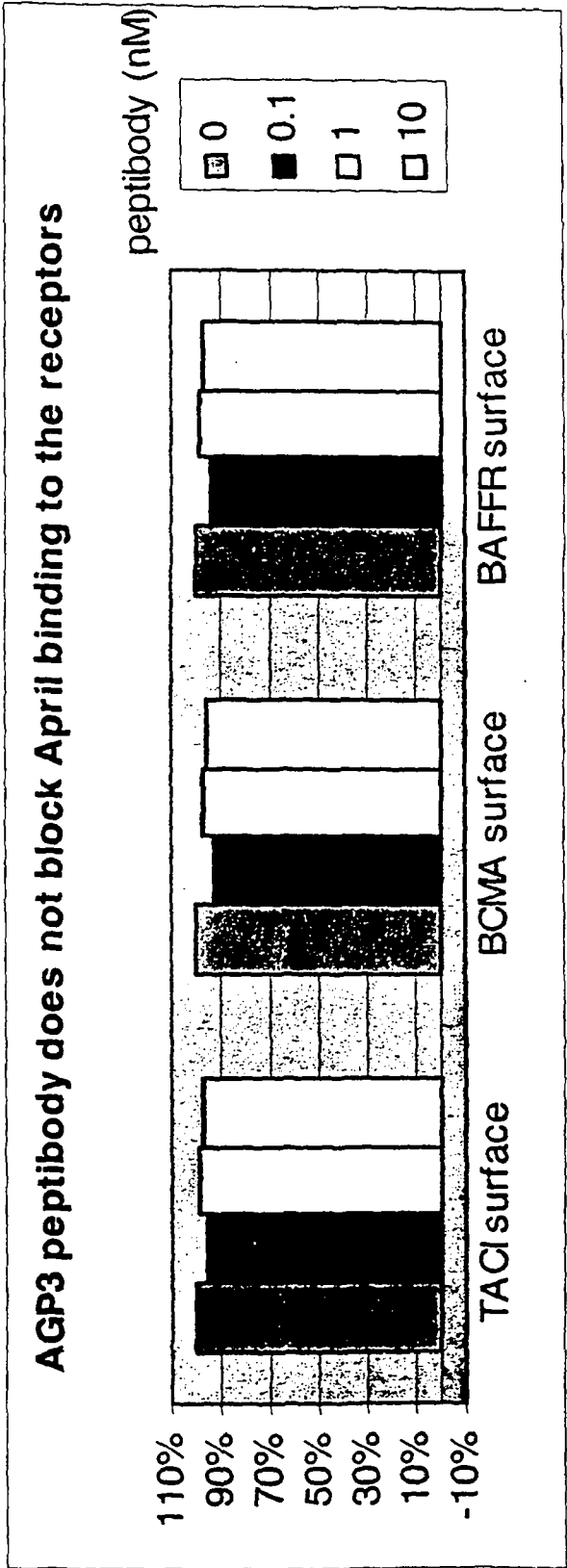


FIG. 12B

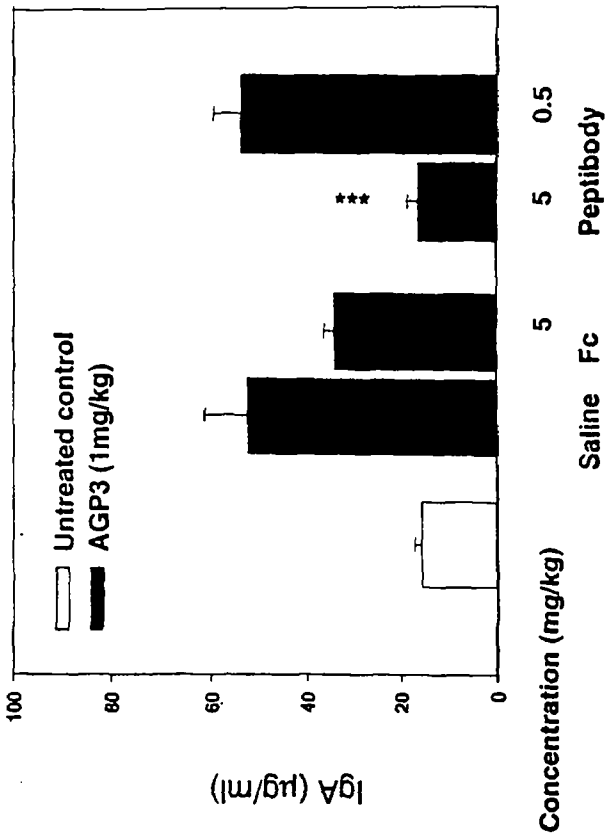


FIG. 12A

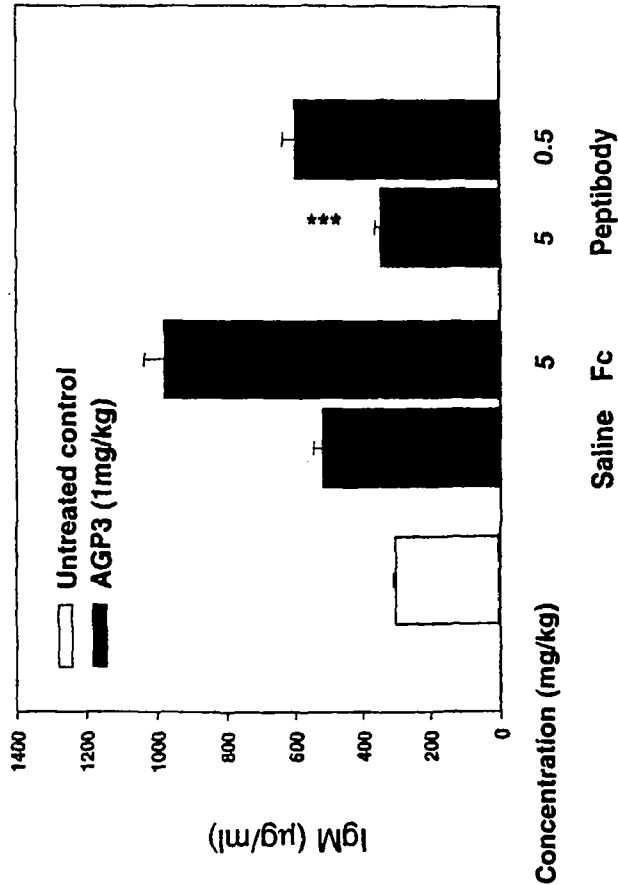
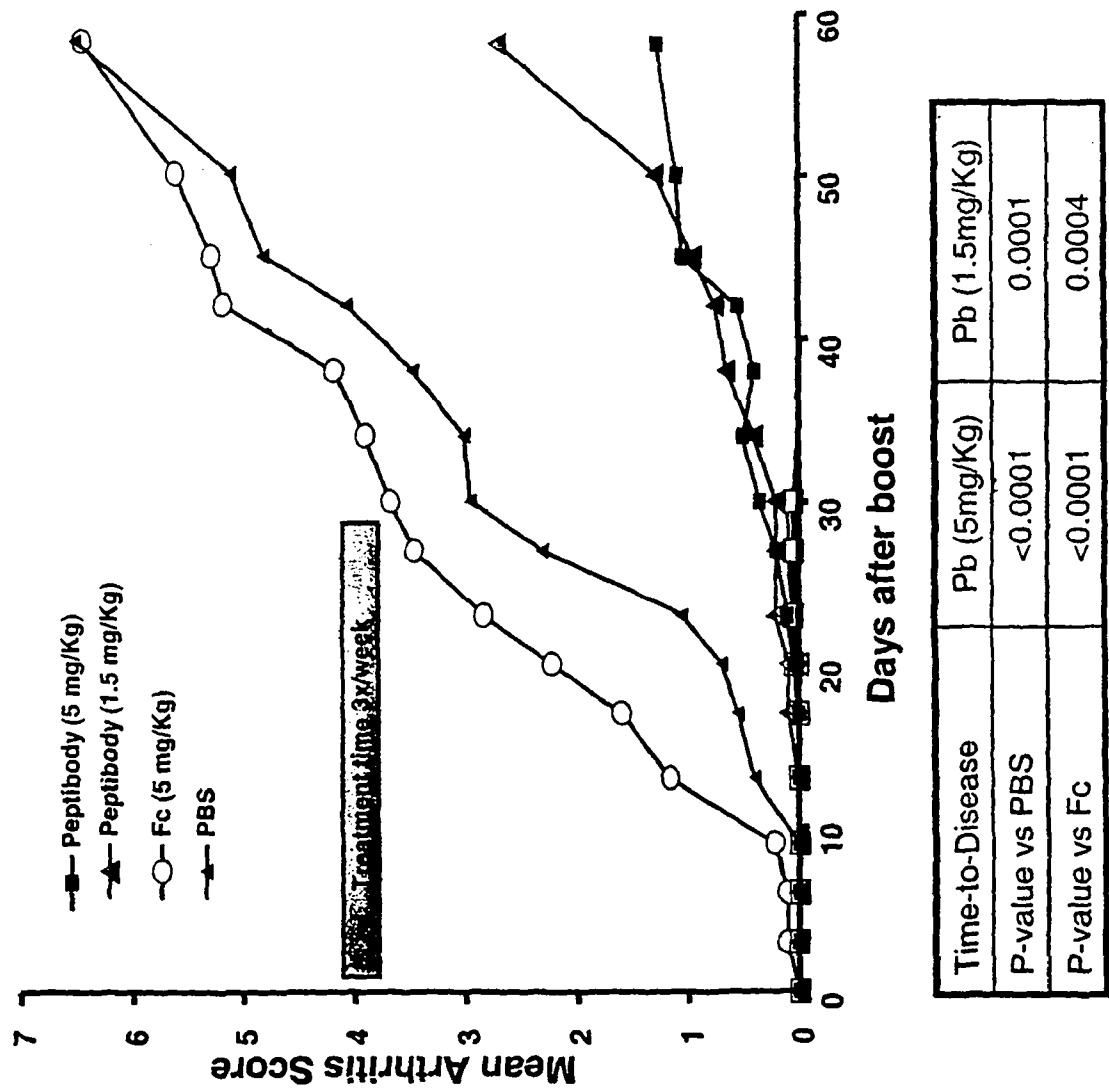


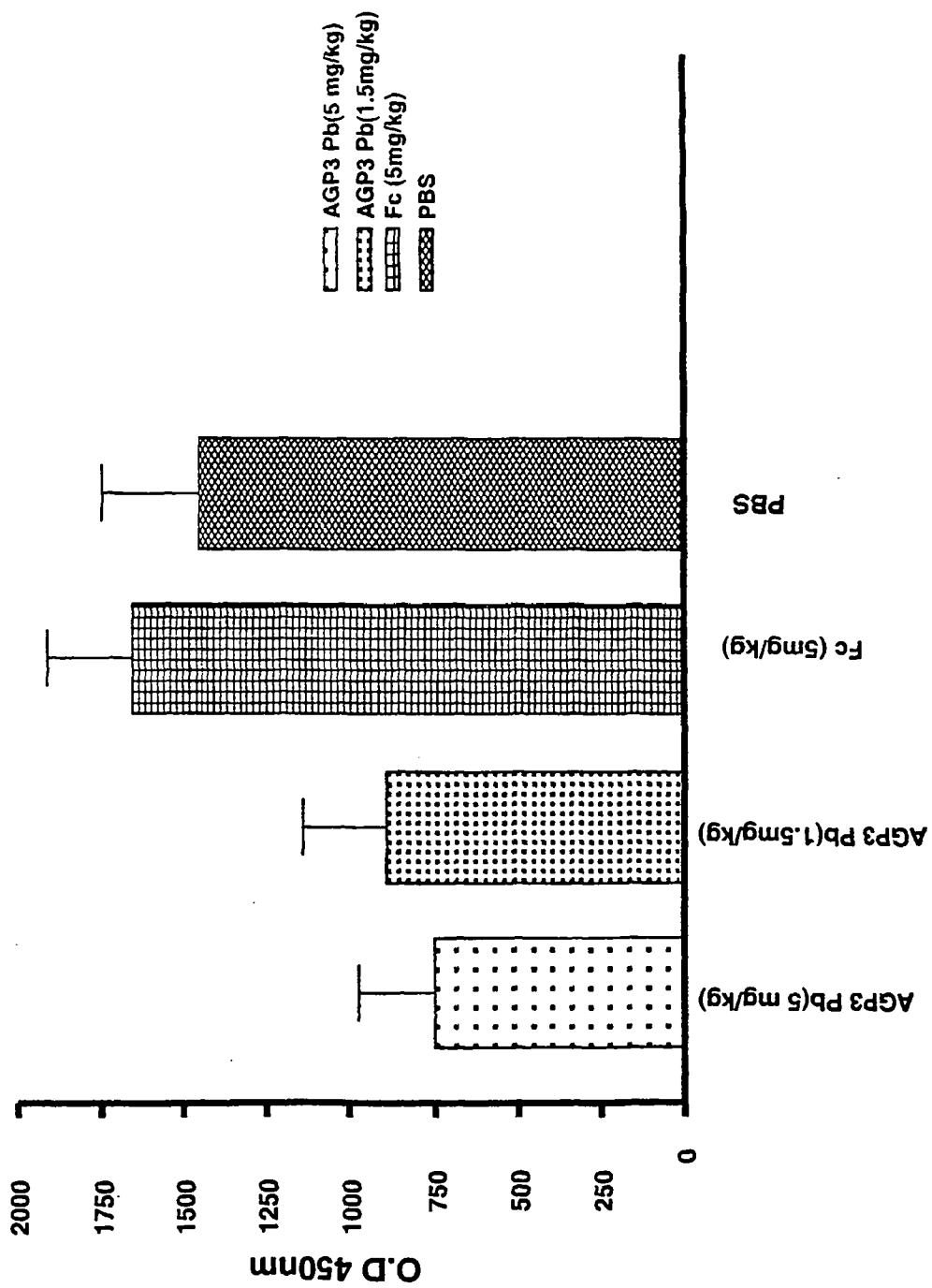
FIG. 13



Note: p-value based on log-rank test

FIG. 14

Reduced anti-collagen IgG2b upon
treatment with AGP3 peptibody

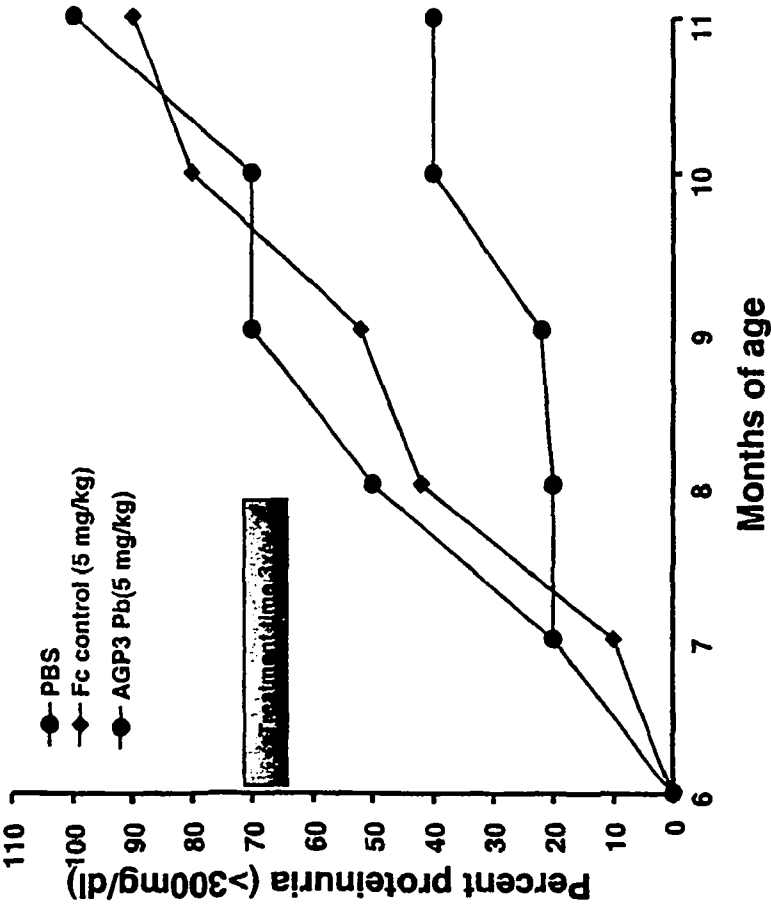


Serum samples were taken one week after final treatment of reagent (day 35).

The graph above is representative of the IgG1, IgG3, and IgG2a isotypes as well.

Fig. 15A

Delayed proteinuria with AGP3 protein blockers

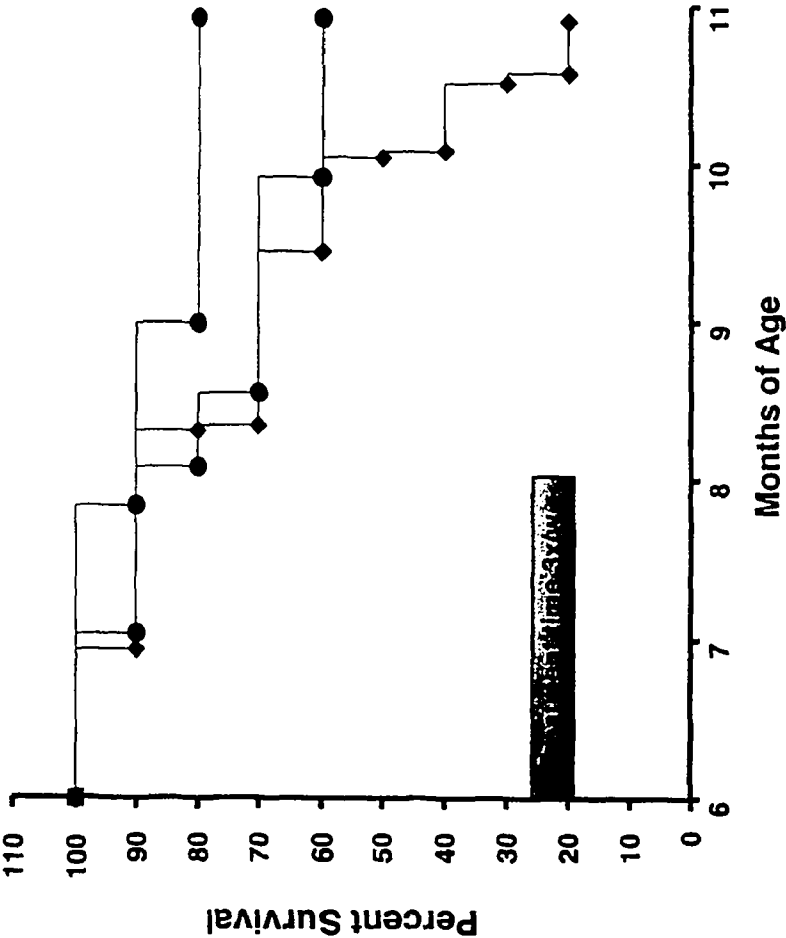


Proteinuria Incidence	Pb
p-value vs PBS	0.0108
P-vs Fc	0.0573

P-value based Fisher's Exact test

Fig. 15B

Prolonged survival with AGP3 blockers



Time-to-Death	Pb
p-value vs PBS	0.3685
p-value vs Fc	0.0159

P-value based log-rank test

FIG. 16A

BamHI
|

1 ATGCTTCCAGGCTGCAAGTGGGATCTTCTTATTAAGCAATGGGTATGCGATCCACTTGGA
-----+-----+-----+-----+-----+ 60
TACGAAGGTCCGACGTTACCCCTAGAAGAATAATTCGTTACCCATACGCTAGGTGAACCT

M L P G C K W D L L I K Q W V C D P L G -

61 TCCGGTTCTGCTACTGGTGGTTCCGGCTCCACCGCAAGCTCTGGTTCAGGCAGTGCGACT
-----+-----+-----+-----+-----+ 120
AGGCCAAGACGATGACCACCAAGGCCGAGGTGGCGTTCGAGACCAAGTCCGTCACGCTGA

S G S A T G G S G S T A S S G S G S A T -

NdeI
|

121 CATATGCTGCCGGGTTGTAAATGGGACCTGCTGATCAAACAGTGGGTTTGTGACCCGCTG
-----+-----+-----+-----+-----+ 180
GTATACGACGGCCCAACATTTACCCTGGACGACTAGTTTGTACCCAAACACTGGGCGAC

H M L P G C K W D L L I K Q W V C D P L -

SalI
|

181 GGTGGAGGCGGTGGGGTCGACAAACTCACACATGTCCACCTTGTCAGCTCCGGAACCT
-----+-----+-----+-----+-----+ 240
CCACCTCCGCCACCCCAGCTGTTTTGAGTGTGTACAGGTGGAACAGGTCGAGGCCTTGAG

G G G G G V D K T H T C P P C P A P E L -

241 CTGGGGGGACCGTCAGTCTTCTCTTCCCCCAAACCCAAGGACACCCTCATGATCTCC
-----+-----+-----+-----+-----+ 300
GACCCCCCTGGCAGTCAGAAGGAGAAGGGGGGTTTTGGGTTCTGTGGGAGTACTAGAGG

L G G P S V F L F P P K P K D T L M I S -

301 CGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAG
-----+-----+-----+-----+-----+ 360
GCCTGGGGACTCCAGTGTACGCACCAACCTGCACTCGGTGCTTCTGGGACTCCAGTTC

R T P E V T C V V V D V S H E D P E V K -

361 TTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAG
-----+-----+-----+-----+-----+ 420
AAGTTGACCATGCACCTGCCGCACCTCCACGTATTACGGTTCTGTTTCGGCGCCCTCCTC

F N W Y V D G V E V H N A K T K P R E E -

421 CAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTG
-----+-----+-----+-----+-----+ 480
GTCATGTTGTCTGTCATGGCACACCAGTCGCAGGAGTGGCAGGACGTGGTCTGACCGAC

Q Y N S T Y R V V S V L T V L H Q D W L -

AATGGCAAGGAGTACAAGTGCAGGCTTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAA
 481 -----+-----+-----+-----+-----+-----+ 540
 TTACCGTTCCTCATGTTACGTTCCAGAGGTTGTTTCGGGAGGGTCGGGGGTAGCTCTTT
 N G K E Y K C K V S N K A L P A P I E K -
 ACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCC
 541 -----+-----+-----+-----+-----+-----+ 600
 TGGTAGAGGTTTCGGTTTCCCGTCGGGGCTCTTGGTGTCCACATGTGGGACGGGGGTAGG
 T I S K A K G Q P R E P Q V Y T L P P S -
 CGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCC
 601 -----+-----+-----+-----+-----+-----+ 660
 GCCCTACTCGACTGGTTCTTGGTCCAGTCGGAAGTGGACCGGACAGTTTCCGAAGATAGGG
 R D E L T K N Q V S L T C L V K G F Y P -
 AGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACG
 661 -----+-----+-----+-----+-----+-----+ 720
 TCGCTGTAGCGGCACCTCACCTCTCGTTACCCGTCGGCCTCTTGTGATGTTCTGGTGC
 S D I A V E W E S N G Q P E N N Y K T T -
 CCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAG
 721 -----+-----+-----+-----+-----+-----+ 780
 GGAGGGCACGACCTGAGGCTGCCGAGGAAGAAGGAGATGTCGTTTCGAGTGGCACCTGTTT
 P P V L D S D G S F F L Y S K L T V D K -
 AGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAAC
 781 -----+-----+-----+-----+-----+-----+ 840
 TCGTCCACCGTCGTCCCCTTGCAGAAGAGTACGAGGCACTACGTACTCCGAGACGTGTTG
 S R W Q Q G N V F S C S V M H E A L H N -
 CACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATAA
 841 -----+-----+-----+-----+-----+-----+ 882
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 H Y T Q K S L S L S P G K * -

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ggg gga ccg tca gtc ttc ctc ttc ccc cca aaa ccc aag gac acc ctc	96
Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu	
20 25 30	

atg atc tcc cgg acc cct gag gtc aca tgc gtg gtg gtg gac gtg agc	144
Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser	
35 40 45	

cac gaa gac cct gag gtc aag ttc aac tgg tac gtg gac ggc gtg gag	192
His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu	
50 55 60	

gtg cat aat gcc aag aca aag ccg cgg gag gag cag tac aac agc acg	240
Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr	
65 70 75 80	

tac cgt gtg gtc agc gtc ctc acc gtc ctg cac cag gac tgg ctg aat	288
Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn	
85 90 95	

ggc aag gag tac aag tgc aag gtc tcc aac aaa gcc ctc cca gcc ccc	336
Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro	
100 105 110	

atc gag aaa acc atc tcc aaa gcc aaa ggg cag ccc cga gaa cca cag	384
Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln	
115 120 125	

gtg tac acc ctg ccc cca tcc cgg gat gag ctg acc aag aac cag gtc	432
Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val	
130 135 140	

agc ctg acc tgc ctg gtc aaa ggc ttc tat ccc agc gac atc gcc gtg	480
Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val	

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 Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
 165 170 175

ccc gtg ctg gac tcc gac ggc tcc ttc ttc ctc tac agc aag ctc acc 576
 Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
 180 185 190

gtg gac aag agc agg tgg cag cag ggg aac gtc ttc tca tgc tcc gtg 624
 Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
 195 200 205

atg cat gag gct ctg cac aac cac tac acg cag aag agc ctc tcc ctg 672
 Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
 210 215 220

tct ccg ggt aaa 684
 Ser Pro Gly Lys
 225

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Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
 20 25 30

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
 35 40 45

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
 50 55 60

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
 65 70 75 80

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
 85 90 95

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
 100 105 110

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
 115 120 125

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

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
 145 150 155 160

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Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
 165 170 175

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
 180 185 190

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
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Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
 210 215 220

Ser Pro Gly Lys
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 1 5 10 15

gga ggc ggt ggg g 62
 Gly Gly Gly Gly
 20

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Gly Gly Gly Gly
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 1 5 10 15
 gga ggc ggt ggg g 62
 Gly Gly Gly Gly
 20

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Gly Gly Gly Gly
 20

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 1 5 10 15

gga ggc ggt ggg g 62
 Gly Gly Gly Gly
 20

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1				5					10					15	

Gly	Gly	Gly	Gly
			20

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	Met	Gly	Ser	Arg	Cys	Lys	Tyr	Lys	Trp	Asp	Val	Leu	Thr	Lys	Gln	Cys	
	1				5					10					15		

ttc	cac	cac	ggt	gga	ggc	ggt	ggg	g	74
Phe	His	His	Gly	Gly	Gly	Gly	Gly		
							20		

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Met	Gly	Ser	Arg	Cys	Lys	Tyr	Lys	Trp	Asp	Val	Leu	Thr	Lys	Gln	Cys
1				5					10					15	

Phe	His	His	Gly	Gly	Gly	Gly	Gly
							20

<210> 11

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Met	Leu	Pro	Gly	Cys	Lys	Trp	Asp	Leu	Leu	Ile	Lys	Gln	Trp	Val	Cys			
1				5					10					15				

gac	ccg	ctg	ggt	gga	ggc	ggt	ggg	g										74
Asp	Pro	Leu	Gly	Gly	Gly	Gly	Gly											
			20															

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1				5					10					15				

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			20															

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Met	Ser	Ala	Asp	Cys	Tyr	Phe	Asp	Ile	Leu	Thr	Lys	Ser	Asp	Val	Cys			
1				5					10					15				

act	tct	tct	ggt	gga	ggc	ggt	ggg	g										74
Thr	Ser	Ser	Gly	Gly	Gly	Gly	Gly											
			20															

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1				5					10					15				

Thr	Ser	Ser	Gly	Gly	Gly	Gly	Gly											
			20															

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 Met Ser Asp Asp Cys Met Tyr Asp Gln Leu Thr Arg Met Phe Ile Cys
 1 5 10 15

tct aac ctg ggt gga ggc ggt ggg g 74
 Ser Asn Leu Gly Gly Gly Gly Gly
 20

<210> 16
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 1 5 10 15

Ser Asn Leu Gly Gly Gly Gly Gly
 20

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 Met Asp Leu Asn Cys Lys Tyr Asp Glu Leu Thr Tyr Lys Glu Trp Cys
 1 5 10 15

cag ttc aac ggg gtg gag gcg gtg ggg 76
 Gln Phe Asn Gly Val Glu Ala Val
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 1 5 10 15

Gln Phe Asn Gly Val Glu Ala Val
 20

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 1385 1390 1395
 Thr Gly Ala Thr Ala Gly Cys Gly Ala Ala Ala Gly Cys Cys Thr
 1400 1405 1410

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Gly Gly Cys Gly Thr Thr Thr Thr Gly Thr Thr Cys Gly Thr Gly
 1415 1420 1425
 Ala Gly Cys Gly Thr Thr Thr Thr Cys Gly Cys Ala Gly Thr Thr
 1430 1435 1440
 Ala Thr Cys Ala Gly Ala Cys Ala Gly Ala Gly Cys Thr Thr Ala
 1445 1450 1455
 Ala Gly Thr Cys Cys Cys Gly Thr Gly Gly Ala Ala Thr Ala Ala
 1460 1465 1470
 Ala Gly Cys Gly Thr Gly Cys Cys Cys Gly Thr Gly Cys Gly Cys
 1475 1480 1485
 Gly Thr Cys Gly Thr Gly Ala Thr Gly Cys Gly Gly Ala Cys Ala
 1490 1495 1500
 Gly Gly Gly Ala Ala Cys Gly Thr Cys Ala Gly Gly Ala Thr Ala
 1505 1510 1515
 Thr Thr Gly Thr Cys Ala Cys Cys Cys Thr Gly Gly Thr Gly Ala
 1520 1525 1530
 Ala Ala Cys Gly Gly Cys Ala Gly Cys Thr Gly Ala Cys Gly Cys
 1535 1540 1545
 Gly Cys Gly Ala Ala Ala Thr Cys Gly Cys Gly Gly Ala Ala Gly
 1550 1555 1560
 Gly Gly Cys Gly Cys Thr Thr Cys Ala Cys Thr Gly Cys Cys Ala
 1565 1570 1575
 Ala Thr Cys Gly Thr Gly Ala Gly Gly Cys Gly Gly Thr Ala Ala
 1580 1585 1590
 Ala Ala Cys Gly Cys Gly Ala Ala Gly Thr Thr Gly Ala Gly Cys
 1595 1600 1605
 Gly Thr Cys Gly Thr Gly Thr Gly Ala Ala Gly Gly Ala Gly Cys
 1610 1615 1620
 Gly Cys Ala Thr Gly Ala Thr Thr Cys Thr Gly Thr Cys Ala Cys
 1625 1630 1635
 Gly Thr Ala Ala Cys Cys Gly Thr Ala Ala Thr Thr Ala Cys Ala
 1640 1645 1650
 Gly Cys Cys Gly Gly Cys Thr Gly Gly Cys Cys Ala Cys Ala Gly
 1655 1660 1665

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Cys Thr Thr Cys Cys Cys Cys Cys Thr Gly Ala Ala Ala Gly Thr
 1670 1675 1680
 Gly Ala Cys Cys Thr Cys Cys Thr Cys Thr Gly Ala Ala Thr Ala
 1685 1690 1695
 Ala Thr Cys Cys Gly Gly Cys Cys Thr Gly Cys Gly Cys Cys Gly
 1700 1705 1710
 Gly Ala Gly Gly Cys Thr Thr Cys Cys Gly Cys Ala Cys Gly Thr
 1715 1720 1725
 Cys Thr Gly Ala Ala Gly Cys Cys Cys Gly Ala Cys Ala Gly Cys
 1730 1735 1740
 Gly Cys Ala Cys Ala Ala Ala Ala Ala Ala Thr Cys Ala Gly Cys
 1745 1750 1755
 Ala Cys Cys Ala Cys Ala Thr Ala Cys Ala Ala Ala Ala Ala Ala
 1760 1765 1770
 Cys Ala Ala Cys Cys Thr Cys Ala Thr Cys Ala Thr Cys Cys Ala
 1775 1780 1785
 Gly Cys Thr Thr Cys Thr Gly Gly Thr Gly Cys Ala Thr Cys Cys
 1790 1795 1800
 Gly Gly Cys Cys Cys Cys Cys Cys Cys Thr Gly Thr Thr Thr Thr
 1805 1810 1815
 Cys Gly Ala Thr Ala Cys Ala Ala Ala Ala Cys Ala Cys Gly Cys
 1820 1825 1830
 Cys Thr Cys Ala Cys Ala Gly Ala Cys Gly Gly Gly Gly Ala Ala
 1835 1840 1845
 Thr Thr Thr Thr Gly Cys Thr Thr Ala Thr Cys Cys Ala Cys Ala
 1850 1855 1860
 Thr Thr Ala Ala Ala Cys Thr Gly Cys Ala Ala Gly Gly Gly Ala
 1865 1870 1875
 Cys Thr Thr Cys Cys Cys Cys Ala Thr Ala Ala Gly Gly Thr Thr
 1880 1885 1890
 Ala Cys Ala Ala Cys Cys Gly Thr Thr Cys Ala Thr Gly Thr Cys
 1895 1900 1905
 Ala Thr Ala Ala Ala Gly Cys Gly Cys Cys Ala Thr Cys Cys Gly
 1910 1915 1920

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Cys Cys Ala Gly Cys Gly Thr Thr Ala Cys Ala Gly Gly Gly Thr
 1925 1930 1935
 Gly Cys Ala Ala Thr Gly Thr Ala Thr Cys Thr Thr Thr Thr Ala
 1940 1945 1950
 Ala Ala Cys Ala Cys Cys Thr Gly Thr Thr Thr Ala Thr Ala Thr
 1955 1960 1965
 Cys Thr Cys Cys Thr Thr Thr Ala Ala Ala Cys Thr Ala Cys Thr
 1970 1975 1980
 Thr Ala Ala Thr Thr Ala Cys Ala Thr Thr Cys Ala Thr Thr Thr
 1985 1990 1995
 Ala Ala Ala Ala Ala Gly Ala Ala Ala Ala Cys Cys Thr Ala Thr
 2000 2005 2010
 Thr Cys Ala Cys Thr Gly Cys Cys Thr Gly Thr Cys Cys Thr Thr
 2015 2020 2025
 Gly Gly Ala Cys Ala Gly Ala Cys Ala Gly Ala Thr Ala Thr Gly
 2030 2035 2040
 Cys Ala Cys Cys Thr Cys Cys Cys Ala Cys Cys Gly Cys Ala Ala
 2045 2050 2055
 Gly Cys Gly Gly Cys Gly Gly Gly Cys Cys Cys Cys Thr Ala Cys
 2060 2065 2070
 Cys Gly Gly Ala Gly Cys Cys Gly Cys Thr Thr Thr Ala Gly Thr
 2075 2080 2085
 Thr Ala Cys Ala Ala Cys Ala Cys Thr Cys Ala Gly Ala Cys Ala
 2090 2095 2100
 Cys Ala Ala Cys Cys Ala Cys Cys Ala Gly Ala Ala Ala Ala Ala
 2105 2110 2115
 Cys Cys Cys Cys Gly Gly Thr Cys Cys Ala Gly Cys Gly Cys Ala
 2120 2125 2130
 Gly Ala Ala Cys Thr Gly Ala Ala Ala Cys Cys Ala Cys Ala Ala
 2135 2140 2145
 Ala Gly Cys Cys Cys Cys Thr Cys Cys Cys Thr Cys Ala Thr Ala
 2150 2155 2160
 Ala Cys Thr Gly Ala Ala Ala Ala Gly Cys Gly Gly Cys Cys Cys
 2165 2170 2175

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Cys Gly Cys Cys Cys Cys Gly Gly Thr Cys Cys Gly Ala Ala Gly
 2180 2185 2190
 Gly Gly Cys Cys Gly Gly Ala Ala Cys Ala Gly Ala Gly Thr Cys
 2195 2200 2205
 Gly Cys Thr Thr Thr Thr Ala Ala Thr Thr Ala Thr Gly Ala Ala
 2210 2215 2220
 Thr Gly Thr Thr Gly Thr Ala Ala Cys Thr Ala Cys Thr Thr Cys
 2225 2230 2235
 Ala Thr Cys Ala Thr Cys Gly Cys Thr Gly Thr Cys Ala Gly Thr
 2240 2245 2250
 Cys Thr Thr Cys Thr Cys Gly Cys Thr Gly Gly Ala Ala Gly Thr
 2255 2260 2265
 Thr Cys Thr Cys Ala Gly Thr Ala Cys Ala Cys Gly Cys Thr Cys
 2270 2275 2280
 Gly Thr Ala Ala Gly Cys Gly Gly Cys Cys Cys Thr Gly Ala Cys
 2285 2290 2295
 Gly Gly Cys Cys Cys Gly Cys Thr Ala Ala Cys Gly Cys Gly Gly
 2300 2305 2310
 Ala Gly Ala Thr Ala Cys Gly Cys Cys Cys Cys Gly Ala Cys Thr
 2315 2320 2325
 Thr Cys Gly Gly Gly Thr Ala Ala Ala Cys Cys Cys Thr Cys Gly
 2330 2335 2340
 Thr Cys Gly Gly Gly Ala Cys Cys Ala Cys Thr Cys Cys Gly Ala
 2345 2350 2355
 Cys Cys Gly Cys Gly Cys Ala Cys Ala Gly Ala Ala Gly Cys Thr
 2360 2365 2370
 Cys Thr Cys Thr Cys Ala Thr Gly Gly Cys Thr Gly Ala Ala Ala
 2375 2380 2385
 Gly Cys Gly Gly Gly Thr Ala Thr Gly Gly Thr Cys Thr Gly Gly
 2390 2395 2400
 Cys Ala Gly Gly Gly Cys Thr Gly Gly Gly Gly Ala Thr Gly Gly
 2405 2410 2415
 Gly Thr Ala Ala Gly Gly Thr Gly Ala Ala Ala Thr Cys Thr Ala
 2420 2425 2430

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Thr	Cys	Ala	Ala	Thr	Cys	Ala	Gly	Thr	Ala	Cys	Cys	Gly	Gly	Cys
2435						2440					2445			
Thr	Thr	Ala	Cys	Gly	Cys	Cys	Gly	Gly	Gly	Cys	Thr	Thr	Cys	Gly
2450						2455					2460			
Gly	Cys	Gly	Gly	Thr	Thr	Thr	Thr	Ala	Cys	Thr	Cys	Cys	Thr	Gly
2465						2470					2475			
Thr	Thr	Thr	Cys	Ala	Thr	Ala	Thr	Ala	Thr	Gly	Ala	Ala	Ala	Cys
2480						2485					2490			
Ala	Ala	Cys	Ala	Gly	Gly	Thr	Cys	Ala	Cys	Cys	Gly	Cys	Cys	Thr
2495						2500					2505			
Thr	Cys	Cys	Ala	Thr	Gly	Cys	Cys	Gly	Cys	Thr	Gly	Ala	Thr	Gly
2510						2515					2520			
Cys	Gly	Gly	Cys	Ala	Thr	Ala	Thr	Cys	Cys	Thr	Gly	Gly	Thr	Ala
2525						2530					2535			
Ala	Cys	Gly	Ala	Thr	Ala	Thr	Cys	Thr	Gly	Ala	Ala	Thr	Thr	Gly
2540						2545					2550			
Thr	Thr	Ala	Thr	Ala	Cys	Ala	Thr	Gly	Thr	Gly	Thr	Ala	Thr	Ala
2555						2560					2565			
Thr	Ala	Cys	Gly	Thr	Gly	Gly	Thr	Ala	Ala	Thr	Gly	Ala	Cys	Ala
2570						2575					2580			
Ala	Ala	Ala	Ala	Thr	Ala	Gly	Gly	Ala	Cys	Ala	Ala	Gly	Thr	Thr
2585						2590					2595			
Ala	Ala	Ala	Ala	Ala	Thr	Thr	Thr	Ala	Cys	Ala	Gly	Gly	Cys	Gly
2600						2605					2610			
Ala	Thr	Gly	Cys	Ala	Ala	Thr	Gly	Ala	Thr	Thr	Cys	Ala	Ala	Ala
2615						2620					2625			
Cys	Ala	Cys	Gly	Thr	Ala	Ala	Thr	Cys	Ala	Ala	Thr	Ala	Thr	Cys
2630						2635					2640			
Gly	Gly	Gly	Gly	Gly	Thr	Gly	Gly	Gly	Cys	Gly	Ala	Ala	Gly	Ala
2645						2650					2655			
Ala	Cys	Thr	Cys	Cys	Ala	Gly	Cys	Ala	Thr	Gly	Ala	Gly	Ala	Thr
2660						2665					2670			
Cys	Cys	Cys	Cys	Gly	Cys	Gly	Cys	Thr	Gly	Gly	Ala	Gly	Gly	Ala
2675						2680					2685			

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Thr	Cys	Ala	Thr	Cys	Cys	Ala	Gly	Cys	Cys	Gly	Gly	Cys	Gly	Thr
2690						2695					2700			
Cys	Cys	Cys	Gly	Gly	Ala	Ala	Ala	Ala	Cys	Gly	Ala	Thr	Thr	Cys
2705						2710					2715			
Cys	Gly	Ala	Ala	Gly	Cys	Cys	Cys	Ala	Ala	Cys	Cys	Thr	Thr	Thr
2720						2725					2730			
Cys	Ala	Thr	Ala	Gly	Ala	Ala	Gly	Gly	Cys	Gly	Gly	Cys	Gly	Gly
2735						2740					2745			
Thr	Gly	Gly	Ala	Ala	Thr	Cys	Gly	Ala	Ala	Ala	Thr	Cys	Thr	Cys
2750						2755					2760			
Gly	Thr	Gly	Ala	Thr	Gly	Gly	Cys	Ala	Gly	Gly	Thr	Thr	Gly	Gly
2765						2770					2775			
Gly	Cys	Gly	Thr	Cys	Gly	Cys	Thr	Thr	Gly	Gly	Thr	Cys	Gly	Gly
2780						2785					2790			
Thr	Cys	Ala	Thr	Thr	Thr	Cys	Gly	Ala	Ala	Cys	Cys	Cys	Cys	Ala
2795						2800					2805			
Gly	Ala	Gly	Thr	Cys	Cys	Cys	Gly	Cys	Thr	Cys	Ala	Gly	Ala	Ala
2810						2815					2820			
Gly	Ala	Ala	Cys	Thr	Cys	Gly	Thr	Cys	Ala	Ala	Gly	Ala	Ala	Gly
2825						2830					2835			
Gly	Cys	Gly	Ala	Thr	Ala	Gly	Ala	Ala	Gly	Gly	Cys	Gly	Ala	Thr
2840						2845					2850			
Gly	Cys	Gly	Cys	Thr	Gly	Cys	Gly	Ala	Ala	Thr	Cys	Gly	Gly	Gly
2855						2860					2865			
Ala	Gly	Cys	Gly	Gly	Cys	Gly	Ala	Thr	Ala	Cys	Cys	Gly	Thr	Ala
2870						2875					2880			
Ala	Ala	Gly	Cys	Ala	Cys	Gly	Ala	Gly	Gly	Ala	Ala	Gly	Cys	Gly
2885						2890					2895			
Gly	Thr	Cys	Ala	Gly	Cys	Cys	Cys	Ala	Thr	Thr	Cys	Gly	Cys	Cys
2900						2905					2910			
Gly	Cys	Cys	Ala	Ala	Gly	Cys	Thr	Cys	Thr	Thr	Cys	Ala	Gly	Cys
2915						2920					2925			
Ala	Ala	Thr	Ala	Thr	Cys	Ala	Cys	Gly	Gly	Gly	Thr	Ala	Gly	Cys
2930						2935					2940			

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Cys Ala Ala Cys Gly Cys Thr Ala Thr Gly Thr Cys Cys Thr Gly
 2945 2950 2955
 Ala Thr Ala Gly Cys Gly Gly Thr Cys Cys Gly Cys Cys Ala Cys
 2960 2965 2970
 Ala Cys Cys Cys Ala Gly Cys Cys Gly Gly Cys Cys Ala Cys Ala
 2975 2980 2985
 Gly Thr Cys Gly Ala Thr Gly Ala Ala Thr Cys Cys Ala Gly Ala
 2990 2995 3000
 Ala Ala Ala Gly Cys Gly Gly Cys Cys Ala Thr Thr Thr Thr Cys
 3005 3010 3015
 Cys Ala Cys Cys Ala Thr Gly Ala Thr Ala Thr Thr Cys Gly Gly
 3020 3025 3030
 Cys Ala Ala Gly Cys Ala Gly Gly Cys Ala Thr Cys Gly Cys Cys
 3035 3040 3045
 Ala Thr Gly Ala Gly Thr Cys Ala Cys Gly Ala Cys Gly Ala Gly
 3050 3055 3060
 Ala Thr Cys Cys Thr Cys Gly Cys Cys Gly Thr Cys Gly Gly Gly
 3065 3070 3075
 Cys Ala Thr Gly Cys Gly Cys Gly Cys Cys Thr Thr Gly Ala Gly
 3080 3085 3090
 Cys Cys Thr Gly Gly Cys Gly Ala Ala Cys Ala Gly Thr Thr Cys
 3095 3100 3105
 Gly Gly Cys Thr Gly Gly Cys Gly Cys Gly Ala Gly Cys Cys Cys
 3110 3115 3120
 Cys Thr Gly Ala Thr Gly Cys Thr Cys Thr Thr Cys Gly Thr Cys
 3125 3130 3135
 Cys Ala Gly Ala Thr Cys Ala Thr Cys Cys Thr Gly Ala Thr Cys
 3140 3145 3150
 Gly Ala Cys Ala Ala Gly Ala Cys Cys Gly Gly Cys Thr Thr Cys
 3155 3160 3165
 Cys Ala Thr Cys Cys Gly Ala Gly Thr Ala Cys Gly Thr Gly Cys
 3170 3175 3180
 Thr Cys Gly Cys Thr Cys Gly Ala Thr Gly Cys Gly Ala Thr Gly
 3185 3190 3195

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Thr Thr Thr Cys Gly Cys Thr Thr Gly Gly Thr Gly Gly Thr Cys
 3200 3205 3210
 Gly Ala Ala Thr Gly Gly Gly Cys Ala Gly Gly Thr Ala Gly Cys
 3215 3220 3225
 Cys Gly Gly Ala Thr Cys Ala Ala Gly Cys Gly Thr Ala Thr Gly
 3230 3235 3240
 Cys Ala Gly Cys Cys Gly Cys Cys Gly Cys Ala Thr Thr Gly Cys
 3245 3250 3255
 Ala Thr Cys Ala Gly Cys Cys Ala Thr Gly Ala Thr Gly Gly Ala
 3260 3265 3270
 Thr Ala Cys Thr Thr Thr Cys Thr Cys Gly Gly Cys Ala Gly Gly
 3275 3280 3285
 Ala Gly Cys Ala Ala Gly Gly Thr Gly Ala Gly Ala Thr Gly Ala
 3290 3295 3300
 Cys Ala Gly Gly Ala Gly Ala Thr Cys Cys Thr Gly Cys Cys Cys
 3305 3310 3315
 Cys Gly Gly Cys Ala Cys Thr Thr Cys Gly Cys Cys Cys Ala Ala
 3320 3325 3330
 Thr Ala Gly Cys Ala Gly Cys Cys Ala Gly Thr Cys Cys Cys Thr
 3335 3340 3345
 Thr Cys Cys Cys Gly Cys Thr Thr Cys Ala Gly Thr Gly Ala Cys
 3350 3355 3360
 Ala Ala Cys Gly Thr Cys Gly Ala Gly Cys Ala Cys Ala Gly Cys
 3365 3370 3375
 Thr Gly Cys Gly Cys Ala Ala Gly Gly Ala Ala Cys Gly Cys Cys
 3380 3385 3390
 Cys Gly Thr Cys Gly Thr Gly Gly Cys Cys Ala Gly Cys Cys Ala
 3395 3400 3405
 Cys Gly Ala Thr Ala Gly Cys Cys Gly Cys Gly Cys Thr Gly Cys
 3410 3415 3420
 Cys Thr Cys Gly Thr Cys Cys Thr Gly Cys Ala Ala Thr Thr Cys
 3425 3430 3435
 Ala Thr Thr Cys Ala Gly Gly Ala Cys Ala Cys Cys Gly Gly Ala
 3440 3445 3450

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Cys Ala Gly Gly Thr Cys Gly Gly Thr Cys Thr Thr Gly Ala Cys
 3455 3460 3465
 Ala Ala Ala Ala Ala Gly Ala Ala Cys Cys Gly Gly Gly Cys Gly
 3470 3475 3480
 Cys Cys Cys Cys Thr Gly Cys Gly Cys Thr Gly Ala Cys Ala Gly
 3485 3490 3495
 Cys Cys Gly Gly Ala Ala Cys Ala Cys Gly Gly Cys Gly Gly Cys
 3500 3505 3510
 Ala Thr Cys Ala Gly Ala Gly Cys Ala Gly Cys Cys Gly Ala Thr
 3515 3520 3525
 Thr Gly Thr Cys Thr Gly Thr Thr Gly Thr Gly Cys Cys Cys Ala
 3530 3535 3540
 Gly Thr Cys Ala Thr Ala Gly Cys Cys Gly Ala Ala Thr Ala Gly
 3545 3550 3555
 Cys Cys Thr Cys Thr Cys Cys Ala Cys Cys Cys Ala Ala Gly Cys
 3560 3565 3570
 Gly Gly Cys Cys Gly Gly Ala Gly Ala Ala Cys Cys Thr Gly Cys
 3575 3580 3585
 Gly Thr Gly Cys Ala Ala Thr Cys Cys Ala Thr Cys Thr Thr Gly
 3590 3595 3600
 Thr Thr Cys Ala Ala Thr Cys Ala Thr Gly Cys Gly Ala Ala Ala
 3605 3610 3615
 Cys Gly Ala Thr Cys Cys Thr Cys Ala Thr Cys Cys Thr Gly Thr
 3620 3625 3630
 Cys Thr Cys Thr Thr Gly Ala Thr Cys Thr Gly Ala Thr Cys Thr
 3635 3640 3645
 Thr Gly Ala Thr Cys Cys Cys Cys Thr Gly Cys Gly Cys Cys Ala
 3650 3655 3660
 Thr Cys Ala Gly Ala Thr Cys Cys Thr Thr Gly Gly Cys Gly Gly
 3665 3670 3675
 Cys Ala Ala Gly Ala Ala Ala Gly Cys Cys Ala Thr Cys Cys Ala
 3680 3685 3690
 Gly Thr Thr Thr Ala Cys Thr Thr Thr Gly Cys Ala Gly Gly Gly
 3695 3700 3705

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Cys Thr Thr Cys Cys Cys Ala Ala Cys Cys Thr Thr Ala Cys Cys
 3710 3715 3720
 Ala Gly Ala Gly Gly Gly Cys Gly Cys Cys Cys Cys Ala Gly Cys
 3725 3730 3735
 Thr Gly Gly Cys Ala Ala Thr Thr Cys Cys Gly Gly Thr Thr Cys
 3740 3745 3750
 Gly Cys Thr Thr Gly Cys Thr Gly Thr Cys Cys Ala Thr Ala Ala
 3755 3760 3765
 Ala Ala Cys Cys Gly Cys Cys Cys Ala Gly Thr Cys Thr Ala Gly
 3770 3775 3780
 Cys Thr Ala Thr Cys Gly Cys Cys Ala Thr Gly Thr Ala Ala Gly
 3785 3790 3795
 Cys Cys Cys Ala Cys Thr Gly Cys Ala Ala Gly Cys Thr Ala Cys
 3800 3805 3810
 Cys Thr Gly Cys Thr Thr Thr Cys Thr Cys Thr Thr Thr Gly Cys
 3815 3820 3825
 Gly Cys Thr Thr Gly Cys Gly Thr Thr Thr Thr Cys Cys Cys Thr
 3830 3835 3840
 Thr Gly Thr Cys Cys Ala Gly Ala Thr Ala Gly Cys Cys Cys Ala
 3845 3850 3855
 Gly Thr Ala Gly Cys Thr Gly Ala Cys Ala Thr Thr Cys Ala Thr
 3860 3865 3870
 Cys Cys Gly Gly Gly Gly Thr Cys Ala Gly Cys Ala Cys Cys Gly
 3875 3880 3885
 Thr Thr Thr Cys Thr Gly Cys Gly Gly Ala Cys Thr Gly Gly Cys
 3890 3895 3900
 Thr Thr Thr Cys Thr Ala Cys Gly Thr Gly Thr Thr Cys Cys Gly
 3905 3910 3915
 Cys Thr Thr Cys Cys Thr Thr Thr Ala Gly Cys Ala Gly Cys Cys
 3920 3925 3930
 Cys Thr Thr Gly Cys Gly Cys Cys Cys Thr Gly Ala Gly Thr Gly
 3935 3940 3945
 Cys Thr Thr Gly Cys Gly Gly Cys Ala Gly Cys Gly Thr Gly Ala
 3950 3955 3960

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Ala Gly Cys Thr Ala Cys Ala Thr Ala Thr Ala Thr Gly Thr Gly
 3965 3970 3975

Ala Thr Cys Cys Gly Gly Gly Cys Ala Ala Ala Thr Cys Gly Cys
 3980 3985 3990

Thr Gly Ala Ala Thr Ala Thr Thr Cys Cys Thr Thr Thr Thr Gly
 3995 4000 4005

Thr Cys Thr Cys Cys Gly Ala Cys Cys Ala Thr Cys Ala Gly Gly
 4010 4015 4020

Cys Ala Cys Cys Thr Gly Ala Gly Thr Cys Gly Cys Thr Gly Thr
 4025 4030 4035

Cys Thr Thr Thr Thr Cys Gly Thr Gly Ala Cys Ala Thr Thr
 4040 4045 4050

Cys Ala Gly Thr Thr Cys Gly Cys Thr Gly Cys Gly Cys Thr Cys
 4055 4060 4065

Ala Cys Gly Gly Cys Thr Cys Thr Gly Gly Cys Ala Gly Thr Gly
 4070 4075 4080

Ala Ala Thr Gly Gly Gly Gly Gly Thr Ala Ala Ala Thr Gly Gly
 4085 4090 4095

Cys Ala Cys Thr Ala Cys Ala Gly Gly Cys Gly Cys Cys Thr Thr
 4100 4105 4110

Thr Thr Ala Thr Gly Gly Ala Thr Thr Cys Ala Thr Gly Cys Ala
 4115 4120 4125

Ala Gly Gly Ala Ala Ala Cys Thr Ala Cys Cys Cys Ala Thr Ala
 4130 4135 4140

Ala Thr Ala Cys Ala Ala Gly Ala Ala Ala Ala Gly Cys Cys Cys
 4145 4150 4155

Gly Thr Cys Ala Cys Gly Gly Gly Cys Thr Thr Cys Thr Cys Ala
 4160 4165 4170

Gly Gly Gly Cys Gly Thr Thr Thr Thr Ala Thr Gly Gly Cys Gly
 4175 4180 4185

Gly Gly Thr Cys Thr Gly Cys Thr Ala Thr Gly Thr Gly Gly Thr
 4190 4195 4200

Gly Cys Thr Ala Thr Cys Thr Gly Ala Cys Thr Thr Thr Thr Thr
 4205 4210 4215

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Gly Cys Thr Gly Thr Thr Cys Ala Gly Cys Ala Gly Thr Thr Cys
 4220 4225 4230
 Cys Thr Gly Cys Cys Cys Thr Cys Thr Gly Ala Thr Thr Thr Thr
 4235 4240 4245
 Cys Cys Ala Gly Thr Cys Thr Gly Ala Cys Cys Ala Cys Thr Thr
 4250 4255 4260
 Cys Gly Gly Ala Thr Thr Ala Thr Cys Cys Cys Gly Thr Gly Ala
 4265 4270 4275
 Cys Ala Gly Gly Thr Cys Ala Thr Thr Cys Ala Gly Ala Cys Thr
 4280 4285 4290
 Gly Gly Cys Thr Ala Ala Thr Gly Cys Ala Cys Cys Cys Ala Gly
 4295 4300 4305
 Thr Ala Ala Gly Gly Cys Ala Gly Cys Gly Gly Thr Ala Thr Cys
 4310 4315 4320
 Ala Thr Cys Ala Ala Cys Ala Gly Gly Cys Thr Thr Ala Cys Cys
 4325 4330 4335
 Cys Gly Thr Cys Thr Thr Ala Cys Thr Gly Thr Cys Gly Ala Ala
 4340 4345 4350
 Gly Ala Cys Gly Thr Gly Cys Gly Thr Ala Ala Cys Gly Thr Ala
 4355 4360 4365
 Thr Gly Cys Ala Thr Gly Gly Thr Cys Thr Cys Cys Cys Cys Ala
 4370 4375 4380
 Thr Gly Cys Gly Ala Gly Ala Gly Thr Ala Gly Gly Gly Ala Ala
 4385 4390 4395
 Cys Thr Gly Cys Cys Ala Gly Gly Cys Ala Thr Cys Ala Ala Ala
 4400 4405 4410
 Thr Ala Ala Ala Ala Cys Gly Ala Ala Ala Gly Gly Cys Thr Cys
 4415 4420 4425
 Ala Gly Thr Cys Gly Ala Ala Ala Gly Ala Cys Thr Gly Gly Gly
 4430 4435 4440
 Cys Cys Thr Thr Thr Cys Gly Thr Thr Thr Thr Ala Thr Cys Thr
 4445 4450 4455
 Gly Thr Thr Gly Thr Thr Thr Gly Thr Cys Gly Gly Thr Gly Ala
 4460 4465 4470

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Ala Cys Gly Cys Thr Cys Thr Cys Cys Thr Gly Ala Gly Thr Ala
 4475 4480 4485

Gly Gly Ala Cys Ala Ala Ala Thr Cys Cys Gly Cys Cys Gly Gly
 4490 4495 4500

Gly Ala Gly Cys Gly Gly Ala Thr Thr Thr Gly Ala Ala Cys Gly
 4505 4510 4515

Thr Thr Gly Cys Gly Ala Ala Gly Cys Ala Ala Cys Gly Gly Cys
 4520 4525 4530

Cys Cys Gly Gly Ala Gly Gly Gly Thr Gly Gly Cys Gly Gly Gly
 4535 4540 4545

Cys Ala Gly Gly Ala Cys Gly Cys Cys Cys Gly Cys Cys Ala Thr
 4550 4555 4560

Ala Ala Ala Cys Thr Gly Cys Cys Ala Gly Gly Cys Ala Thr Cys
 4565 4570 4575

Ala Ala Ala Thr Thr Ala Ala Gly Cys Ala Gly Ala Ala Gly Gly
 4580 4585 4590

Cys Cys Ala Thr Cys Cys Thr Gly Ala Cys Gly Gly Ala Thr Gly
 4595 4600 4605

Gly Cys Cys Thr Thr Thr Thr Thr Gly Cys Gly Thr Thr Thr Cys
 4610 4615 4620

Thr Ala Cys Ala Ala Ala Cys Thr Cys Thr Thr Thr Thr Gly Thr
 4625 4630 4635

Thr Thr Ala Thr Thr Thr Thr Thr Cys Thr Ala Ala Ala Thr Ala
 4640 4645 4650

Cys Ala Thr Thr Cys Ala Ala Ala Thr Ala Thr Gly Gly Ala Cys
 4655 4660 4665

Gly Thr Cys Gly Thr Ala Cys Thr Thr Ala Ala Cys Thr Thr Thr
 4670 4675 4680

Thr Ala Ala Ala Gly Thr Ala Thr Gly Gly Gly Cys Ala Ala Thr
 4685 4690 4695

Cys Ala Ala Thr Thr Gly Cys Thr Cys Cys Thr Gly Thr Thr Ala
 4700 4705 4710

Ala Ala Ala Thr Thr Gly Cys Thr Thr Thr Ala Gly Ala Ala Ala
 4715 4720 4725

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Thr Ala Cys Thr Thr Thr Gly Gly Cys Ala Gly Cys Gly Gly Thr
 4730 4735 4740
 Thr Thr Gly Thr Thr Gly Thr Ala Thr Thr Gly Ala Gly Thr Thr
 4745 4750 4755
 Thr Cys Ala Thr Thr Thr Gly Cys Gly Cys Ala Thr Thr Gly Gly
 4760 4765 4770
 Thr Thr Ala Ala Ala Thr Gly Gly Ala Ala Ala Gly Thr Gly Ala
 4775 4780 4785
 Cys Cys Gly Thr Gly Cys Gly Cys Thr Thr Ala Cys Thr Ala Cys
 4790 4795 4800
 Ala Gly Cys Cys Thr Ala Ala Thr Ala Thr Thr Thr Thr Thr Gly
 4805 4810 4815
 Ala Ala Ala Thr Ala Thr Cys Cys Cys Ala Ala Gly Ala Gly Cys
 4820 4825 4830
 Thr Thr Thr Thr Thr Cys Cys Thr Thr Cys Gly Cys Ala Thr Gly
 4835 4840 4845
 Cys Cys Cys Ala Cys Gly Cys Thr Ala Ala Ala Cys Ala Thr Thr
 4850 4855 4860
 Cys Thr Thr Thr Thr Thr Cys Thr Cys Thr Thr Thr Thr Gly Gly
 4865 4870 4875
 Thr Thr Ala Ala Ala Thr Cys Gly Thr Thr Gly Thr Thr Thr Gly
 4880 4885 4890
 Ala Thr Thr Thr Ala Thr Thr Ala Thr Thr Thr Gly Cys Thr Ala
 4895 4900 4905
 Thr Ala Thr Thr Thr Ala Thr Thr Thr Thr Thr Cys Gly Ala Thr
 4910 4915 4920
 Ala Ala Thr Thr Ala Thr Cys Ala Ala Cys Thr Ala Gly Ala Gly
 4925 4930 4935
 Ala Ala Gly Gly Ala Ala Cys Ala Ala Thr Thr Ala Ala Thr Gly
 4940 4945 4950
 Gly Thr Ala Thr Gly Thr Thr Cys Ala Thr Ala Cys Ala Cys Gly
 4955 4960 4965
 Cys Ala Thr Gly Thr Ala Ala Ala Ala Thr Ala Ala Ala Cys
 4970 4975 4980

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Thr Ala Thr Cys Thr Ala Thr Ala Thr Ala Gly Thr Thr Gly Thr
 4985 4990 4995
 Cys Thr Thr Thr Cys Thr Cys Thr Gly Ala Ala Thr Gly Thr Gly
 5000 5005 5010
 Cys Ala Ala Ala Ala Cys Thr Ala Ala Gly Cys Ala Thr Thr Cys
 5015 5020 5025
 Cys Gly Ala Ala Gly Cys Cys Ala Thr Thr Ala Thr Thr Ala Gly
 5030 5035 5040
 Cys Ala Gly Thr Ala Thr Gly Ala Ala Thr Ala Gly Gly Gly Ala
 5045 5050 5055
 Ala Ala Cys Thr Ala Ala Ala Cys Cys Cys Ala Gly Thr Gly Ala
 5060 5065 5070
 Thr Ala Ala Gly Ala Cys Cys Thr Gly Ala Thr Gly Ala Thr Thr
 5075 5080 5085
 Thr Cys Gly Cys Thr Thr Cys Thr Thr Thr Ala Ala Thr Thr Ala
 5090 5095 5100
 Cys Ala Thr Thr Thr Gly Gly Ala Gly Ala Thr Thr Thr Thr Thr
 5105 5110 5115
 Thr Ala Thr Thr Thr Ala Cys Ala Gly Cys Ala Thr Thr Gly Thr
 5120 5125 5130
 Thr Thr Thr Cys Ala Ala Ala Thr Ala Thr Ala Thr Thr Cys Cys
 5135 5140 5145
 Ala Ala Thr Thr Ala Ala Thr Cys Gly Gly Thr Gly Ala Ala Thr
 5150 5155 5160
 Gly Ala Thr Thr Gly Gly Ala Gly Thr Thr Ala Gly Ala Ala Thr
 5165 5170 5175
 Ala Ala Thr Cys Thr Ala Cys Thr Ala Thr Ala Gly Gly Ala Thr
 5180 5185 5190
 Cys Ala Thr Ala Thr Thr Thr Thr Ala Thr Thr Ala Ala Ala Thr
 5195 5200 5205
 Thr Ala Gly Cys Gly Thr Cys Ala Thr Cys Ala Thr Ala Ala Thr
 5210 5215 5220
 Ala Thr Thr Gly Cys Cys Thr Cys Cys Ala Thr Thr Thr Thr Thr
 5225 5230 5235

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Thr Ala Gly Gly Gly Thr Ala Ala Thr Thr Ala Thr Cys Cys Ala
 5240 5245 5250
 Gly Ala Ala Thr Thr Gly Ala Ala Ala Thr Ala Thr Cys Ala Gly
 5255 5260 5265
 Ala Thr Thr Thr Ala Ala Cys Cys Ala Thr Ala Gly Ala Ala Thr
 5270 5275 5280
 Gly Ala Gly Gly Ala Thr Ala Ala Ala Thr Gly Ala Thr Cys Gly
 5285 5290 5295
 Cys Gly Ala Gly Thr Ala Ala Ala Thr Ala Ala Thr Ala Thr Thr
 5300 5305 5310
 Cys Ala Cys Ala Ala Thr Gly Thr Ala Cys Cys Ala Thr Thr Thr
 5315 5320 5325
 Thr Ala Gly Thr Cys Ala Thr Ala Thr Cys Ala Gly Ala Thr Ala
 5330 5335 5340
 Ala Gly Cys Ala Thr Thr Gly Ala Thr Thr Ala Ala Thr Ala Thr
 5345 5350 5355
 Cys Ala Thr Thr Ala Thr Thr Gly Cys Thr Thr Cys Thr Ala Cys
 5360 5365 5370
 Ala Gly Gly Cys Thr Thr Thr Ala Ala Thr Thr Thr Thr Ala Thr
 5375 5380 5385
 Thr Ala Ala Thr Thr Ala Thr Thr Cys Thr Gly Thr Ala Ala Gly
 5390 5395 5400
 Thr Gly Thr Cys Gly Thr Cys Gly Gly Cys Ala Thr Thr Thr Ala
 5405 5410 5415
 Thr Gly Thr Cys Thr Thr Thr Cys Ala Thr Ala Cys Cys Cys Ala
 5420 5425 5430
 Thr Cys Thr Cys Thr Thr Thr Ala Thr Cys Cys Thr Thr Ala Cys
 5435 5440 5445
 Cys Thr Ala Thr Thr Gly Thr Thr Thr Gly Thr Cys Gly Cys Ala
 5450 5455 5460
 Ala Gly Thr Thr Thr Thr Gly Cys Gly Thr Gly Thr Thr Ala Thr
 5465 5470 5475
 Ala Thr Ala Thr Cys Ala Thr Thr Ala Ala Ala Ala Cys Gly Gly
 5480 5485 5490

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Thr Ala Ala Thr Ala Gly Ala Thr Thr Gly Ala Cys Ala Thr Thr
 5495 5500 5505
 Thr Gly Ala Thr Thr Cys Thr Ala Ala Thr Ala Ala Ala Thr Thr
 5510 5515 5520
 Gly Gly Ala Thr Thr Thr Thr Thr Gly Thr Cys Ala Cys Ala Cys
 5525 5530 5535
 Thr Ala Thr Thr Ala Thr Ala Thr Cys Gly Cys Thr Thr Gly Ala
 5540 5545 5550
 Ala Ala Thr Ala Cys Ala Ala Thr Thr Gly Thr Thr Thr Ala Ala
 5555 5560 5565
 Cys Ala Thr Ala Ala Gly Thr Ala Cys Cys Thr Gly Thr Ala Gly
 5570 5575 5580
 Gly Ala Thr Cys Gly Thr Ala Cys Ala Gly Gly Thr Thr Thr Ala
 5585 5590 5595
 Cys Gly Cys Ala Ala Gly Ala Ala Ala Ala Thr Gly Gly Thr Thr
 5600 5605 5610
 Thr Gly Thr Thr Ala Thr Ala Gly Thr Cys Gly Ala Thr Thr Ala
 5615 5620 5625
 Ala Thr Cys Gly Ala Thr Thr Thr Gly Ala Thr Thr Cys Thr Ala
 5630 5635 5640
 Gly Ala Thr Thr Thr Gly Thr Thr Thr Thr Ala Ala Cys Thr Ala
 5645 5650 5655
 Ala Thr Thr Ala Ala Ala Gly Gly Ala Gly Gly Ala Ala Thr Ala
 5660 5665 5670
 Ala Cys Ala Thr Ala Thr Gly Ala Thr Cys Gly Cys Thr Cys Cys
 5675 5680 5685
 Ala Cys Cys Ala Thr Gly Cys Ala Cys Cys Ala Gly Thr Gly Ala
 5690 5695 5700
 Gly Ala Ala Gly Cys Ala Thr Thr Ala Thr Gly Ala Gly Cys Ala
 5705 5710 5715
 Thr Cys Thr Gly Gly Gly Ala Cys Gly Gly Thr Gly Cys Thr Gly
 5720 5725 5730
 Thr Ala Ala Cys Ala Ala Ala Thr Gly Thr Gly Ala Ala Cys Cys
 5735 5740 5745

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Ala	Gly	Gly	Ala	Ala	Ala	Gly	Thr	Ala	Cys	Ala	Thr	Gly	Thr	Cys
	5750					5755					5760			
Thr	Thr	Cys	Thr	Ala	Ala	Ala	Thr	Gly	Cys	Ala	Cys	Thr	Ala	Cys
	5765					5770					5775			
Thr	Ala	Cys	Cys	Thr	Cys	Thr	Gly	Ala	Cys	Ala	Gly	Thr	Gly	Thr
	5780					5785					5790			
Ala	Thr	Gly	Thr	Cys	Thr	Gly	Cys	Cys	Cys	Thr	Gly	Thr	Gly	Gly
	5795					5800					5805			
Cys	Cys	Cys	Gly	Gly	Ala	Thr	Gly	Ala	Ala	Thr	Ala	Cys	Thr	Thr
	5810					5815					5820			
Gly	Gly	Ala	Thr	Ala	Gly	Cys	Thr	Gly	Gly	Ala	Ala	Thr	Gly	Ala
	5825					5830					5835			
Ala	Gly	Ala	Ala	Gly	Ala	Thr	Ala	Ala	Ala	Thr	Gly	Cys	Thr	Thr
	5840					5845					5850			
Gly	Cys	Thr	Gly	Cys	Ala	Thr	Ala	Ala	Ala	Gly	Thr	Thr	Thr	Gly
	5855					5860					5865			
Thr	Gly	Ala	Thr	Ala	Cys	Ala	Gly	Gly	Cys	Ala	Ala	Gly	Gly	Cys
	5870					5875					5880			
Cys	Cys	Thr	Gly	Gly	Thr	Gly	Gly	Cys	Cys	Gly	Thr	Gly	Gly	Thr
	5885					5890					5895			
Cys	Gly	Cys	Cys	Gly	Gly	Cys	Ala	Ala	Cys	Ala	Gly	Thr	Ala	Cys
	5900					5905					5910			
Gly	Ala	Cys	Cys	Cys	Cys	Cys	Cys	Gly	Gly	Cys	Gly	Cys	Thr	Gly
	5915					5920					5925			
Cys	Gly	Cys	Gly	Thr	Gly	Cys	Ala	Cys	Gly	Gly	Cys	Thr	Gly	Gly
	5930					5935					5940			
Gly	Thr	Ala	Cys	Cys	Ala	Cys	Thr	Gly	Gly	Ala	Gly	Cys	Cys	Ala
	5945					5950					5955			
Gly	Gly	Ala	Cys	Thr	Gly	Cys	Gly	Ala	Gly	Thr	Gly	Cys	Thr	Gly
	5960					5965					5970			
Cys	Cys	Gly	Cys	Cys	Gly	Cys	Ala	Ala	Cys	Ala	Cys	Cys	Gly	Ala
	5975					5980					5985			
Gly	Thr	Gly	Cys	Gly	Cys	Gly	Cys	Cys	Gly	Gly	Gly	Cys	Cys	Thr
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Gly Gly Gly Cys Gly Cys Cys Cys Ala Gly Cys Ala Cys Cys Cys
 6005 6010 6015
 Gly Thr Thr Gly Cys Ala Gly Cys Thr Cys Ala Ala Cys Ala Ala
 6020 6025 6030
 Gly Gly Ala Cys Ala Cys Ala Gly Thr Gly Thr Gly Cys Ala Ala
 6035 6040 6045
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 6050 6055 6060
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 6065 6070 6075
 Cys Thr Thr Thr Thr Cys Cys Thr Cys Cys Ala Cys Gly Gly Ala
 6080 6085 6090
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 6095 6100 6105
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 6215 6220 6225
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 6230 6235 6240
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Thr Cys Cys Gly Gly Ala Ala Cys Thr Cys Cys Thr Gly Gly Gly
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 6290                               6295                               6300

Ala Cys Cys Cys Ala Ala Gly Gly Ala Cys Ala Cys Cys Cys Thr
 6305                               6310                               6315

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 6395                               6400                               6405

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 6470                               6475                               6480

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Cys Ala Ala Gly Gly Ala Gly Thr Ala Cys Ala Ala Gly Thr Gly
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 6545 6550 6555

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Cys Thr Cys Cys Ala Ala Ala Gly Cys Cys Ala Ala Ala Gly Gly
 6575 6580 6585

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 6605 6610 6615

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 6650 6655 6660

Cys Thr Gly Cys Cys Thr Gly Gly Thr Cys Ala Ala Ala Gly Gly
 6665 6670 6675

Cys Thr Thr Cys Thr Ala Thr Cys Cys Cys Ala Gly Cys Gly Ala
 6680 6685 6690

Cys Ala Thr Cys Gly Cys Cys Gly Thr Gly Gly Ala Gly Thr Gly
 6695 6700 6705

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 6725 6730 6735

Cys Ala Ala Gly Ala Cys Cys Ala Cys Gly Cys Cys Thr Cys Cys
 6740 6745 6750

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 6755 6760 6765

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Cys Gly Gly Cys Thr Cys Cys Thr Thr Cys Thr Thr Cys Cys Thr
 6770 6775 6780
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 6830 6835 6840
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 6875 6880 6885
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 6890 6895 6900
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 7010 7015 7020

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 7055 7060 7065
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 7085 7090 7095
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 7100 7105 7110
 Thr Cys Cys Ala Thr Cys Thr Gly Gly Ala Thr Thr Thr Gly Thr
 7115 7120 7125
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 7130 7135 7140
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 7145 7150 7155
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 7160 7165 7170
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 7175 7180 7185
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 7190 7195 7200
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 Cys Cys Cys Cys Ala Thr Thr Cys Ala Ala Gly Ala Ala Cys Ala
 7220 7225 7230
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 7235 7240 7245
 Ala Ala Cys Thr Thr Thr Gly Gly Ala Ala Thr Cys Cys Ala Gly
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 7265 7270 7275

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<210> 30
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
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Trp Gly Ala Cys Trp Pro Phe Pro Trp Glu Cys Phe Lys Glu
1 5 10

<210> 31
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
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<400> 31

Val Pro Phe Cys Asp Leu Leu Thr Lys His Cys Phe Glu Ala
1 5 10

<210> 32
<211> 18
<212> PRT
<213> Artificial Sequence

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<400> 32

Gly Ser Arg Cys Lys Tyr Lys Trp Asp Val Leu Thr Lys Gln Cys Phe
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His His

<210> 33
<211> 18
<212> PRT

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<213> Artificial Sequence

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<223> Preferred TALL-1 Modulating Domains

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Pro Leu

<210> 34

<211> 18

<212> PRT

<213> Artificial Sequence

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<210> 35

<211> 18

<212> PRT

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1 5 10 15

Asn Leu

<210> 36

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Preferred TALL-1 Modulating Domains

<400> 36

Asp Leu Asn Cys Lys Tyr Asp Glu Leu Thr Tyr Lys Glu Trp Cys Gln
1 5 10 15

Phe Asn

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<210> 37
 <211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
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<400> 37

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Gly Leu

<210> 38
 <211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Preferred TALL-1 Modulating Domains

<400> 38

Arg	Asn	His	Cys	Phe	Trp	Asp	His	Leu	Leu	Lys	Gln	Asp	Ile	Cys	Pro
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Ser Pro

<210> 39
 <211> 18
 <212> PRT
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<220>
 <223> Preferred TALL-1 Modulating Domains

<400> 39

Ala	Asn	Gln	Cys	Trp	Trp	Asp	Ser	Leu	Thr	Lys	Lys	Asn	Val	Cys	Glu
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Phe Phe

<210> 40
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<220>
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<400> 40
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<210> 41

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<211> 8
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<210> 42
 <211> 8
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Polyglycine linkers

<400> 42
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<210> 43
 <211> 5
 <212> PRT
 <213> Artificial Sequence

<220>
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<400> 43

Gly Pro Asn Gly Gly
 1 5

<210> 44
 <211> 19
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Peptide Bond

<220>
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 <223> Xaa = a peptide bond
 Fc domain attached at Position 19 to C-terminus

<400> 44

Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln Trp Val Cys Asp
 1 5 10 15

Pro Leu Xaa

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<210> 45
 <211> 19
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Peptide bond

<220>
 <221> misc_feature
 <222> (1)..(1)
 <223> Xaa = a peptide bond
 Fc domain attached at Position 1 to N-terminus

<400> 45

Xaa Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln Trp Val Cys
 1 5 10 15

Asp Pro Leu

<210> 46
 <211> 38
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Peptide bond

<220>
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 <222> (38)..(38)
 <223> Xaa = a peptide bond
 Fc domain attached at Position 38 to C-terminus

<220>
 <221> misc_feature
 <222> (19)..(19)
 <223> Xaa = a peptide bond

<400> 46

Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln Trp Val Cys Asp
 1 5 10 15

Pro Leu Xaa Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln Trp
 20 25 30

Val Cys Asp Pro Leu Xaa
 35

<210> 47
 <211> 38
 <212> PRT
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<222> (1)..(1)
<223> Xaa = a peptide bond
Fc domain attached at Position 1 to N-terminus

<220>
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<222> (20)..(20)
<223> Xaa = a peptide bond

<400> 47

Xaa Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln Trp Val Cys
1 5 10 15

Asp Pro Leu Xaa Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln
20 25 30

Trp Val Cys Asp Pro Leu
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<210> 48
<211> 19
<212> PRT
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<220>
<223> Peptide bond

<220>
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<222> (19)..(19)
<223> Xaa = a peptide bond
Fc domain attached at Position 19 to C-terminus

<400> 48

Ser Ala Asp Cys Tyr Phe Asp Ile Leu Thr Lys Ser Asp Val Cys Thr
1 5 10 15

Ser Ser Xaa

<210> 49
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<212> PRT
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<220>
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<220>
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<223> Xaa = a peptide bond
Fc domain attached at Position 1 to N-terminus

<400> 49

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Xaa Ser Ala Asp Cys Tyr Phe Asp Ile Leu Thr Lys Ser Asp Val Cys
 1 5 10 15

Thr Ser Ser

<210> 50
 <211> 36
 <212> PRT
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<220>
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<220>
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 <222> (36)..(36)
 <223> Xaa = a peptide bond
 Fc domain attached at Position 36 to C-terminus

<220>
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 <222> (18)..(18)
 <223> Xaa = a peptide bond

<400> 50

Ser Ala Asp Cys Tyr Phe Asp Ile Leu Thr Lys Ser Asp Val Thr Ser
 1 5 10 15

Ser Xaa Ser Ala Asp Cys Tyr Phe Asp Ile Leu Thr Lys Ser Asp Val
 20 25 30

Thr Ser Ser Xaa
 35

<210> 51
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 <212> PRT
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<220>
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<220>
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 <222> (1)..(1)
 <223> Xaa = a peptide bond
 Fc domain attached at Position 1 to N-terminus

<220>
 <221> misc_feature
 <222> (19)..(19)
 <223> Xaa = a peptide bond

<400> 51

Xaa Ser Ala Asp Cys Tyr Phe Asp Ile Leu Thr Lys Ser Asp Val Thr
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1 5 10 15
Ser Ser Xaa Ser Ala Asp Cys Tyr Phe Asp Ile Leu Thr Lys Ser Asp
 20 25 30

Val Thr Ser Ser
 35

<210> 52
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide bond

<220>
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<223> Xaa = a peptide bond
Fc domain attached at Position 19 to C-terminus

<400> 52

Phe His Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Cys His
1 5 10 15

Gly Leu Xaa

<210> 53
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide bond

<220>
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<222> (1)..(1)
<223> Xaa = a peptide bond
Fc domain attached at Position 1 to N-terminus

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1 5 10 15

His Gly Leu

<210> 54
<211> 38
<212> PRT
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<220>
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A-743 PCT.ST25.txt

<220>
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 <222> (19)..(19)
 <223> Xaa = a peptide bond

<220>
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 <222> (38)..(38)
 <223> Xaa = a peptide bond
 Fc domain attached at Position 38 to C-terminus

<400> 54

Phe His Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Cys His
 1 5 10 15

Gly Leu Xaa Phe His Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln Trp
 20 25 30

Val Cys His Gly Leu Xaa
 35

<210> 55
 <211> 38
 <212> PRT
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<220>
 <223> Peptide bond

<220>
 <221> misc_feature
 <222> (1)..(1)
 <223> Xaa = a peptide bond
 Fc domain attached at Position 1 to N-terminus

<220>
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 <222> (20)..(20)
 <223> Xaa = a peptide bond

<400> 55

Xaa Phe His Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Cys
 1 5 10 15

His Gly Leu Xaa Phe His Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln
 20 25 30

Trp Val Cys His Gly Leu
 35

<210> 56
 <211> 25
 <212> DNA
 <213> Artificial Sequence

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<220>

<223> Oligonucleotide

<400> 56

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25

<210> 57

<211> 26

<212> DNA

<213> Artificial Sequence

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<223> Oligonucleotide

<400> 57

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26

<210> 58

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Consensus peptide

<400> 58

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Gly Leu

<210> 59

<211> 23

<212> PRT

<213> Artificial Sequence

<220>

<223> Preferred linker sequence

<400> 59

Gly	Ser	Gly	Ser	Ala	Thr	Gly	Gly	Ser	Gly	Ser	Thr	Ala	Ser	Ser	Gly
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Ser	Gly	Ser	Ala	Thr	His	Met
				20		

<210> 60

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Preferred TALL-1 modulating domains

<400> 60

Asn	Gln	Thr	Leu	Trp	Lys	Trp	Asp	Leu	Leu	Thr	Lys	Gln	Phe	Ile	Thr
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Tyr Met

<210> 61
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 61

Pro	Val	Tyr	Gln	Gly	Trp	Trp	Asp	Thr	Leu	Thr	Lys	Leu	Tyr	Ile	Trp
1				5					10					15	

Asp Gly

<210> 62
<211> 18
<212> PRT
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<220>
<223> Preferred TALL-1 modulating domains

<400> 62

Trp	Leu	Asp	Gly	Gly	Trp	Arg	Asp	Pro	Leu	Ile	Lys	Arg	Ser	Val	Gln
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Leu Gly

<210> 63
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 63

Gly	His	Gln	Gln	Phe	Lys	Trp	Asp	Leu	Leu	Thr	Lys	Gln	Trp	Val	Gln
1				5					10					15	

Ser Asn

<210> 64
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 64

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Gln Arg Val Gly Gln Phe Trp Asp Val Leu Thr Lys Met Phe Ile Thr
 1 5 10 15

Gly Ser

<210> 65
 <211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Preferred TALL-1 modulating domains

<400> 65

Gln Ala Gln Gly Trp Ser Tyr Asp Ala Leu Ile Lys Thr Trp Ile Arg
 1 5 10 15

Trp Pro

<210> 66
 <211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Preferred TALL-1 modulating domains

<400> 66

Gly Trp Met His Trp Lys Trp Asp Pro Leu Thr Lys Gln Ala Leu Pro
 1 5 10 15

Trp Met

<210> 67
 <211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Preferred TALL-1 modulating domains

<400> 67

Gly His Pro Thr Tyr Lys Trp Asp Leu Leu Thr Lys Gln Trp Ile Leu
 1 5 10 15

Gln Met

<210> 68
 <211> 18
 <212> PRT
 <213> Artificial Sequence

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<220>

<223> Preferred TALL-1 modulating domains

<400> 68

Trp Asn Asn Trp Ser Leu Trp Asp Pro Leu Thr Lys Leu Trp Leu Gln
 1 5 10 15

Gln Asn

<210> 69

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Preferred TALL-1 modulating domains

<400> 69

Trp Gln Trp Gly Trp Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Gln
 1 5 10 15

Gln Gln

<210> 70

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Preferred TALL-1 modulating domains

<400> 70

Gly Gln Met Gly Trp Arg Trp Asp Pro Leu Thr Lys Met Trp Leu Gly
 1 5 10 15

Thr Ser

<210> 71

<211> 62

<212> DNA

<213> Artificial Sequence

<220>

<223> Oligonucleotides

<400> 71

tatgccgggt acttgtttcc cgttcccgtg ggaatgcact cacgctgggtg gaggcgggtgg 60

gg 62

<210> 72

<211> 64

<212> DNA

<213> Artificial Sequence

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<220>

<223> Oligonucleotides

<400> 72

tcgacccac cgcctcctgg agcgtgagtg cattcccacg ggaagccgaa acaagtaccc 60

ggca 64

<210> 73

<211> 62

<212> DNA

<213> Artificial Sequence

<220>

<223> Oligonucleotides

<400> 73

tatgtggggg gcttggtggc cgttcccgtg ggaatgtttc aaagaagggtg gaggcggtgg 60

gg 62

<210> 74

<211> 64

<212> DNA

<213> Artificial Sequence

<220>

<223> Oligonucleotides

<400> 74

tcgacccac cgcctccacc ttctttgaaa cattcccacg ggaacggcca acaagcacc 60

caca 64

<210> 75

<211> 62

<212> DNA

<213> Artificial Sequence

<220>

<223> Oligonucleotides

<400> 75

tatggttccg ttctgtgacc tgctgactaa aactgtttc gaagctggtg gaggcggtgg 60

gg 62

<210> 76

<211> 64

<212> DNA

<213> Artificial Sequence

<220>

<223> Oligonucleotides

<400> 76

tcgacccac cgcctccacc agcttcgaaa cagtgtttag tcagcaggtc acagaacgga 60

acca 64

<210> 77

<211> 74

<212> DNA

A-743 PCT.ST25.txt

<213> Artificial Sequence

<220>

<223> Oligonucleotides

<400> 77

tatgggttct cgttgtaaata acaaattggga cgttctgact aaacagtgtt tccaccacgg 60

tggaggcggt gggg 74

<210> 78

<211> 76

<212> DNA

<213> Artificial Sequence

<220>

<223> Oligonucleotides

<400> 78

tcgacccac cgctccacc gtggtggaaa cactgttttag tcagaacgtc ccatttgtat 60

ttacaacgag aaccca 76

<210> 79

<211> 74

<212> DNA

<213> Artificial Sequence

<220>

<223> Oligonucleotides

<400> 79

tatgtctgccg gggttgtaaata gggacctgct gatcaaacag tgggtttgtg acccgctggg 60

tggaggcggt gggg 74

<210> 80

<211> 76

<212> DNA

<213> Artificial Sequence

<220>

<223> Oligonucleotides

<400> 80

tcgacccac cgctccacc cagcgggtca caaacccact gtttgatcag cagggtcccat 60

ttacaacccg gcagca 76

<210> 81

<211> 74

<212> DNA

<213> Artificial Sequence

<220>

<223> Oligonucleotides

<400> 81

tatgtctgct gactgttact tcgacatcct gactaaatct gacgtttgta cttcttctgg 60

tggaggcggt gggg 74

<210> 82

A-743 PCT.ST25.txt

<211> 76
 <212> DNA
 <213> Artificial Sequence

 <220>
 <223> Oligonucleotides

 <400> 82
 tcgacccac cgcctccacc agaagaagta caaacgtcag atttagtcag gatgtcgaag 60
 taacagtcag cagaca 76

<210> 83
 <211> 74
 <212> DNA
 <213> Artificial Sequence

 <220>
 <223> Oligonucleotides

 <400> 83
 tatgtctgac gactgtatgt acgaccagct gactcgtatg ttcattctgtt ctaacctggg 60
 tggaggcggt gggg 74

<210> 84
 <211> 76
 <212> DNA
 <213> Artificial Sequence

 <220>
 <223> Oligonucleotides

 <400> 84
 tcgacccac cgcctccacc caggtagaa cagatgaaca tacgagtcag ctggtcgtac 60
 atacagtcgt cagaca 76

<210> 85
 <211> 74
 <212> DNA
 <213> Artificial Sequence

 <220>
 <223> Oligonucleotides

 <400> 85
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 tggaggcggt gggg 74

<210> 86
 <211> 76
 <212> DNA
 <213> Artificial Sequence

 <220>
 <223> Oligonucleotides

 <400> 86
 tcgacccac cgcctccacc gttgaactga caccattctt tgtaagtcag ttcgtcgtat 60
 ttacagttca ggtcca 76

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<210> 87
<211> 74
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 87
tatgttccac gactgtaa at acgacctgct gactcgtcag atggtttgtc acggctctggg 60
tggaggcggt gggg 74

<210> 88
<211> 76
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 88
tcgacccac cgctccacc cagaccgtga caaacatct gacgagtcag caggctctat 60
ttacagtcgt ggaaca 76

<210> 89
<211> 74
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 89
tatgcgtaac cactgtttct gggaccacct gctgaaacag gacatctgtc cgtctccggg 60
tggaggcggt gggg 74

<210> 90
<211> 76
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 90
tcgacccac cgctccacc cggagacgga cagatgtcct gtttcagcag gtgggtcccag 60
aaacagtggg tacgca 76

<210> 91
<211> 74
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 91
tatggctaac cagtgttggg gggactctct gctgaaaaaa aacgtttgtg aattcttcgg 60

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tggaggcggt gggg

74

<210> 92
 <211> 76
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Oligonucleotides

<400> 92
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 caacactggt tagcca 76

<210> 93
 <211> 74
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Oligonucleotides

<400> 93
 tatgttcac gactgcaaat gggacctgct gaccaaacag tgggtttgcc acggtctggg 60
 tggaggcggt gggg 74

<210> 94
 <211> 76
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Oligonucleotides

<400> 94
 tcgacccac cgcctccacc cagaccgtgg caaacccact gtttggtcag caggtcccat 60
 ttgcagtcgt ggaaca 76

<210> 95
 <211> 141
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> pAMG21-RANK-Fc vector

<400> 95
 ctaattccgc tctcacctac caaacaatgc cccctgcaa aaaataaatt catataaaaa 60
 acatacagat aaccatctgc ggtgataaat tatctctggc ggtgttgaca taaataccac 120
 tggcggtgat actgagcaca t 141

<210> 96
 <211> 55
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> pAMG21-RANK-Fc vector

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<400> 96
 cgatttgatt ctagaaggag gaataacata tggttaacgc gttggaattc ggtac 55

<210> 97
 <211> 1546
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> pAMG21

<400> 97
 gcgtaacgta tgcattggtct ccccatgcga gagtagggaa ctgccaggca tcaaataaaa 60
 cgaaaggctc agtcgaaaga ctgggccttt cgttttatct gttgtttgtc ggtgaacgct 120
 ctcttgagta ggacaaatcc gccgggagcg gatttgaacg ttgcgaagca acggcccgga 180
 ggggtggcggg caggacgccc gccataaact gccaggcatc aaattaagca gaaggccatc 240
 ctgacggatg gcctttttgc gtttctacaa actcttttgt ttatttttct aaatacatc 300
 aaatatggac gtcgtactta acttttaag tatgggcaat caattgctcc tgttaaaatt 360
 gcttttagaaa tactttggca gcggtttgtt gtattgagtt tcatttgcg attggttaaa 420
 tggaaagtga ccgtgcgctt actacagcct aatatttttg aaatatccca agagcttttt 480
 ccttcgcatg cccacgctaa acattctttt tctcttttg ttaaactcgtt gtttgattta 540
 ttatttgcta tattttattt tcgataatta tcaactagag aaggaacaat taatggtatg 600
 ttcatcacg catgtaaaaa taaactatct atatagttgt ctttctctga atgtgcaaaa 660
 ctaagcattc cgaagccatt attagcagta tgaataggga aactaaacc agtgataaga 720
 cctgatgatt tcgcttcttt aattacattt ggagattttt tatttacagc attgttttca 780
 aatatattcc aattaatcgg tgaatgattg gagttagaat aatctactat aggatcatat 840
 tttattaaat tagcgtcatc ataattatgc ctccattttt tagggtaatt atccagaatt 900
 gaaatatcag atttaaccat agaatgagga taaatgatcg cgagtaaata atattcacia 960
 tgtaccattt tagtcatatc agataagcat tgattaatat cattattgct tctacaggct 1020
 ttaattttat taattattct gtaagtgtcg tcggcattta tgtctttcat acccatctct 1080
 ttatccttac ctattgtttg tcgcaagttt tgcgtgttat atatcattaa aacggtaata 1140
 gattgacatt tgattctaata aaattggatt tttgtcacac tattatatcg cttgaaatac 1200
 aattgtttta cataagtacc tgtaggatcg tacaggttta cgcaagaaaa tggtttggtta 1260
 tagtcgatta atcgatttga ttctagattt gttttaacta attaaaggag gaataacata 1320
 tggttaacgc gttggaattc gagctcacta gtgtcgacct gcagggtacc atggaagctt 1380
 actcgaggat ccgcggaaaag aagaagaaga agaagaaagc ccgaaaggaa gctgagttgg 1440
 ctgctgccac cgctgagcaa taactagcat aacccttgg gcctctaaa cgggtcttga 1500
 ggggtttttt gctgaaagga ggaaccgctc ttcacgctct tcacgc 1546

<210> 98

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<211> 872
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> GM221

<400> 98
 ttatttttcgt gcggccgcac cattatcacc gccagaggta aactagtcaa cacgcacggt 60
 gttagatatt tatcccttgc ggtgatagat tgagcacatc gatttgattc tagaaggagg 120
 gataatatat gagcacaaaa aagaaacat taacacaaga gcagcttgag gacgcacgtc 180
 gccttaaagc aatttatgaa aaaaagaaaa atgaacttgg cttatcccag gaatctgtcg 240
 cagacaagat ggggatgggg cagtcaggcg ttggtgcttt atttaatggc atcaatgcat 300
 taaatgctta taacgccgca ttgcttacia aaattctcaa agttagcggt gaagaattta 360
 gcccttcaat cgccagagaa tctacgagat gtatgaagcg gttagtatgc agccgtcact 420
 tagaagtgag tatgagtacc ctgttttttc tcatgttcag gcagggatgt tctcacctaa 480
 gcttagaacc ttaccaaaag gtgatgcgga gagatgggta agcacaacca aaaaagccag 540
 tgattctgca ttctggcttg aggttgaagg taattccatg accgcaccaa cagggtccaa 600
 gccaagcttt cctgacggaa tgtaattct cgttgaccct gagcaggctg ttgagccagg 660
 tgatttctgc atagccagac ttgggggtga tgagtttacc ttcaagaaac tgatcaggga 720
 tagcggtcag gtgtttttac aaccactaaa cccacagtac ccaatgatcc catgcaatga 780
 gagttgttcc gttgtgggga aagttatcgc tagtcagtgg cctgaagaga cgtttggtcg 840
 atagactagt ggatccacta gtgtttctgc cc 872

<210> 99
 <211> 1197
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> GM221

<400> 99
 ggcggaaacc gacgtccatc gaatggtgca aaacctttcg cggtatggca tgatagcgcc 60
 cggaagagag tcaattcagg gtggtgaatg tgaaaccagt aacgttatac gatgtcgag 120
 agtatgccgg tgtctcttat cagaccgttt cccgcgtggg gaaccaggcc agccacgttt 180
 ctgcgaaaac gcgggaaaaa gtcgaagcgg cgatggcgga gctgaattac attcccaacc 240
 gcgtggcaca acaactggcg ggcaaacagt cgctcctgat tggcgttgcc acctccagtc 300
 tggccctgca cgcgccgtcg caaattgtcg cggcgattaa atctcgcgcc gatcaactgg 360
 gtgccagcgt ggtggtgtcg atggtagaac gaagcggcgt cgaagcctgt aaagcggcgg 420
 tgcacaatct tctcgcgcaa cgcgtcagtg ggctgatcat taactatccg ctggatgacc 480
 aggatgccat tgctgtggaa gctgcctgca ctaatgttcc ggcgttatTT cttgatgtct 540
 ctgaccagac acccatcaac agtattatTT tctcccatga agacggtacg cgactgggcg 600

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```

tggagcatct ggtcgcattg ggtcaccagc aaatcgcgct gttagcgggc ccattaagtt    660
ctgtctcggc gcgtctgcgt ctggctggct ggcataaata tctcactcgc aatcaaattc    720
agccgatagc ggaacgggaa ggcgactgga gtgccatgtc cggttttcaa caaaccatgc    780
aaatgctgaa tgagggcatc gttcccactg cgatgctggg tgccaacgat cagatggcgc    840
tgggcgcaat gcgcgccatt accgagtcgg ggctgcgcgt tggcgcgat atctcggtag    900
tgggatacga cgataccgaa gacagctcat gttatatccc gccgttaacc accatcaaac    960
aggattttcg cctgctgggg caaaccagcg tggaccgctt gctgcaactc tctcagggcc   1020
aggcggtgaa gggcaatcag ctgttgcccg tctcactggg gaaaagaaaa accaccctgg   1080
cgccaatac gcaaaccgcc tctccccgcg cgttggccga ttcattaatg cagctggcac   1140
gacaggtttc ccgactggaa agcggacagt aaggtaccat aggatccagg cacagga     1197

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<210> 100
 <211> 14
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Modulators of TALL-1

<220>
 <221> misc_feature
 <222> (1, 2, 3, 13)..(14)
 <223> Xaa (Pos1,2,3,13,14) are each independently absent or amino acid residues;

<220>
 <221> misc_feature
 <222> (6)..(6)
 <223> Xaa (Pos6) is an amino acid residue; Xaa (Pos9) is a basic or hydrophobic residue;

<220>
 <221> misc_feature
 <222> (12)..(12)
 <223> Xaa (Pos12) is a neutral hydrophobic residue.

<400> 100

```

Xaa Xaa Xaa Cys Asp Xaa Leu Thr Xaa Xaa Cys Xaa Xaa Xaa
1           5           10

```

<210> 101
 <211> 14
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Modulators of TALL-1

<220>
 <221> misc_feature
 <222> (1, 2, 3, 12 and)..(13)
 <223> Xaa (Pos1,2,3,12,13) are each independently absent or amino acid

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residues;

<220>
 <221> misc_feature
 <222> (5 and)..(8)
 <223> Xaa (Pos5,8) is a neutral hydrophobic residue; Xaa (Pos10) is an acidic residue;

<220>
 <221> misc_feature
 <222> (14)..(14)
 <223> Xaa (Pos14) is absent or is an amino acid residue.

<400> 101

Xaa Xaa Xaa Cys Xaa Pro Phe Xaa Trp Xaa Cys Xaa Xaa Xaa
 1 5 10

<210> 102
 <211> 14
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Modulator of TALL-1

<220>
 <221> misc_feature
 <222> (1, 2, 3, 12, 13 and)..(14)
 <223> Xaa (Pos1,2,3,12,13,14) are each independently absent or amino acid residues;

<220>
 <221> misc_feature
 <222> (6 and)..(7)
 <223> Xaa (Pos6,7) is a hydrophobic residue;

<220>
 <221> misc_feature
 <222> (10)..(10)
 <223> Xaa (Pos10) is an acidic or polar hydrophobic residue.

<400> 102

Xaa Xaa Xaa Xaa Trp Xaa Xaa Trp Gly Xaa Xaa Xaa Xaa Xaa
 1 5 10

<210> 103
 <211> 14
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Modulator of TALL-1

<220>
 <221> misc_feature
 <222> (1)..(1)
 <223> Xaa (Pos1) is absent or is an amino acid residue;

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<220>
 <221> misc_feature
 <222> (2 and)..(14)
 <223> Xaa (Pos2,14) is a neutral hydrophobic residue;

<220>
 <221> misc_feature
 <222> (3 and)..(10)
 <223> Xaa (Pos3,10) is an amino acid residue;

<220>
 <221> misc_feature
 <222> (5, 6, 7, 8, 12 and)..(13)
 <223> Xaa (Pos5,6,7,8,12,13) are each independently amino acid residues
 ;

<220>
 <221> misc_feature
 <222> (9)..(9)
 <223> Xaa (Pos9) is an acidic residue.

<400> 103

Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa
 1 5 10

<210> 104
 <211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Modulator of TALL-1

<220>
 <221> misc_feature
 <222> (1, 2, 12, 13, 16, 17 and)..(18)
 <223> Xaa (Pos1,2,12,13,16,17,18) are each independently absent or amino acid residues;

<220>
 <221> misc_feature
 <222> (3)..(3)
 <223> Xaa (Pos3) is an acidic or amide residue;

<220>
 <221> misc_feature
 <222> (5 and)..(8)
 <223> Xaa (Pos5,8) is an amino acid residue;

<220>
 <221> misc_feature
 <222> (6)..(6)
 <223> Xaa (Pos6) is an aromatic residue;

<220>
 <221> misc_feature
 <222> (11)..(11)

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<223> Xaa (Pos11) is a basic residue;

<220>

<221> misc_feature

<222> (14)..(14)

<223> Xaa (Pos14) is a neutral hydrophobic residue.

<400> 104

Xaa	Xaa	Xaa	Cys	Xaa	Xaa	Asp	Xaa	Leu	Thr	Xaa	Xaa	Xaa	Xaa	Cys	Xaa
1				5					10					15	

Xaa Xaa

<210> 105

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Modulator of TALL-1

<220>

<221> misc_feature

<222> (1, 2 and)..(3)

<223> Xaa (Pos1,2,3) are each independently absent or amino acid residues;

<220>

<221> misc_feature

<222> (5, 7, 14 and)..(16)

<223> Xaa (Pos5,7,14,16) is an amino acid residue;

<220>

<221> misc_feature

<222> (10)..(10)

<223> Xaa (Pos10) is a basic residue;

<220>

<221> misc_feature

<222> (11 and)..(12)

<223> Xaa (Pos11,12) are each independently amino acid residues;

<220>

<221> misc_feature

<222> (13 and)..(17)

<223> Xaa (Pos13,17) is a neutral hydrophobic residue;

<220>

<221> misc_feature

<222> (18)..(18)

<223> Xaa (Pos18) is an amino acid residue or is absent.

<400> 105

Xaa	Xaa	Xaa	Cys	Xaa	Asp	Xaa	Leu	Thr	Xaa	Xaa	Xaa	Xaa	Xaa	Cys	Xaa
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

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10

1

5

10

15

Xaa Xaa

```

<210> 106
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Modulator of TALL-1

<220>
<221> misc_feature
<222> (1, 2, 3, 16, 17 and)..(18)
<223> Xaa (Pos1,2,3,16,17,18) are each independently absent or amino ac
id residues;

```

```
<220>
<221> misc_feature
<222> (5, 6, 7, 10, 13 and)..(14)
<223> Xaa (Pos5,6,7,10,13,14) are each independently amino acid residue
s.
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<400> 106

Xaa Xaa Xaa Cys Xaa Xaa Xaa Trp Asp Xaa Leu Thr Xaa Xaa Cys Xaa
1 5 10 15

Xaa Xaa

```

<210> 107
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Modulator of TALL-1

<220>
<221> misc_feature
<222> (1,2,3,15,16,17)..(18)
<223> Xaa (Pos1,2,3,15,16,17,18) are each independently absent or amino
acid residues;

```

```
<220>
<221> misc_feature
<222> (5, 6, 7, 9 and)..(13)
<223> Xaa (Pos 5,6,7,9 13) are each independently amino acid residues;
```

```
<220>
<221> misc_feature
<222> (11)..(11)
<223> Xaa (Pos 11) is T or I; and
```

<400> 107

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Xaa Xaa Xaa Cys Xaa Xaa Xaa Asp Xaa Leu Xaa Lys Xaa Cys Xaa Xaa
 1 5 10 15

Xaa Xaa

<210> 108
 <211> 4
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Modulator of TALL-1

<220>
 <221> misc_feature
 <222> (2)..(2)
 <223> X at (Pos 2) is an amino acid residue

<220>
 <221> misc_feature
 <222> (4)..(4)
 <223> X at (Pos 4) is threonyl or isoleucyl

<400> 108

Asp Xaa Leu Xaa
 1

<210> 109
 <211> 14
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Modulator of TALL-1

<220>
 <221> misc_feature
 <222> (1, 2 and)..(3)
 <223> X at (Pos 1, 2, 3) are absent or are amino acid residues (with on
 e of X1, X2, and X3 preferred to be C when one of X12,
 X13, and X14 is C);

<220>
 <221> misc_feature
 <222> (5)..(5)
 <223> X at (Pos 5) is W, Y, or F (W preferred);

<220>
 <221> misc_feature
 <222> (7)..(7)
 <223> X at (Pos 7) is an amino acid residue (L preferred);

<220>
 <221> misc_feature
 <222> (9)..(9)
 <223> X at (Pos 9) is T or I (T preferred);

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```

<220>
<221> misc_feature
<222> (10)..(10)
<223> X at (Pos 10) is K, R, or H ( K preferred).

<220>
<221> misc_feature
<222> (12)..(12)
<223> X at (Pos 12) is C, a neutral hydrophobic residue, or a basic res
      idue (W, C, or R                preferred);

<220>
<221> misc_feature
<222> (13)..(13)
<223> X at (Post 13) is C, a neutral hydrophobic residue or is absent
      (V preferred);

<220>
<221> misc_feature
<222> (14)..(14)
<223> X at (Pos 14) is any amino acid residue or is absent.

<400> 109

Xaa Xaa Xaa Lys Xaa Asp Xaa Leu Xaa Xaa Gln Xaa Xaa Xaa
1          5          10

<210> 110
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Modulator of TALL-1

<400> 110

Pro Phe Pro Trp Glu
1          5

<210> 111
<211> 248
<212> PRT
<213> Artificial Sequence

<220>
<223> TALL-1 inhibitory peptibodies

<400> 111

Met Pro Gly Thr Cys Phe Pro Phe Pro Trp Glu Cys Thr His Ala Gly
1          5          10          15

Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
20          25          30

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
35          40          45

```

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Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
 50 55 60
 Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
 65 70 75 80
 Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
 85 90 95
 Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
 100 105 110
 Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
 115 120 125
 Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
 130 135 140
 Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
 145 150 155 160
 Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
 165 170 175
 Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
 180 185 190
 Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
 195 200 205
 Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
 210 215 220
 Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
 225 230 235 240
 Ser Leu Ser Leu Ser Pro Gly Lys
 245

<210> 112

<211> 248

<212> PRT

<213> Artificial Sequence

<220>

<223> TALL-1 inhibitory peptibodies

<400> 112

Met Trp Gly Ala Cys Trp Pro Phe Pro Trp Glu Cys Phe Lys Glu Gly
 1 5 10 15

Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
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20

25

30

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
 35 40 45

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
 50 55 60

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
 65 70 75 80

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
 85 90 95

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
 100 105 110

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
 115 120 125

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
 130 135 140

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
 145 150 155 160

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
 165 170 175

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
 180 185 190

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
 195 200 205

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
 210 215 220

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
 225 230 235 240

Ser Leu Ser Leu Ser Pro Gly Lys
 245

<210> 113

<211> 248

<212> PRT

<213> Artificial Sequence

<220>

<223> TALL-1 inhibitory peptibodies

<400> 113

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```

Met Val Pro Phe Cys Asp Leu Leu Thr Lys His Cys Phe Glu Ala Gly
1      5      10      15

Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
20      25      30

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
35      40      45

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
50      55      60

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
65      70      75      80

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
85      90      95

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
100     105     110

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
115     120     125

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
130     135     140

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
145     150     155     160

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
165     170     175

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
180     185     190

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
195     200     205

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
210     215     220

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
225     230     235     240

Ser Leu Ser Leu Ser Pro Gly Lys
245

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<210> 114
 <211> 252
 <212> PRT

A-743 PCT.ST25.txt

<213> Artificial Sequence

<220>

<223> TALL-1 inhibitory peptibodies

<400> 114

Met Gly Ser Arg Cys Lys Tyr Lys Trp Asp Val Leu Thr Lys Gln Cys
 1 5 10 15

Phe His His Gly Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro
 20 25 30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
 35 40 45

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
 50 55 60

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
 65 70 75 80

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
 85 90 95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
 100 105 110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
 115 120 125

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
 130 135 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
 145 150 155 160

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
 165 170 175

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
 180 185 190

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
 195 200 205

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
 210 215 220

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
 225 230 235 240

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys

245

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250

<210> 115
 <211> 252
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> TALL-1 inhibitory peptibodies

<400> 115

Met Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln Trp Val Cys
 1 5 10 15

Asp Pro Leu Gly Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro
 20 25 30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
 35 40 45

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
 50 55 60

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
 65 70 75 80

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
 85 90 95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
 100 105 110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
 115 120 125

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
 130 135 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
 145 150 155 160

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
 165 170 175

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
 180 185 190

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
 195 200 205

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
 210 215 220

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Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
 225 230 235 240

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 245 250

<210> 116
 <211> 252
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> TALL-1 inhibitory peptibodies

<400> 116

Met Ser Ala Asp Cys Tyr Phe Asp Ile Leu Thr Lys Ser Asp Val Cys
 1 5 10 15

Thr Ser Ser Gly Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro
 20 25 30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
 35 40 45

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
 50 55 60

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
 65 70 75 80

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
 85 90 95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
 100 105 110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
 115 120 125

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
 130 135 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
 145 150 155 160

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
 165 170 175

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
 180 185 190

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
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195

200

205

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
 210 215 220

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
 225 230 235 240

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 245 250

<210> 117

<211> 252

<212> PRT

<213> Artificial Sequence

<220>

<223> TALL-1 inhibitory peptibodies

<400> 117

Met Ser Asp Asp Cys Met Tyr Asp Gln Leu Thr Arg Met Phe Ile Cys
 1 5 10 15

Ser Asn Leu Gly Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro
 20 25 30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
 35 40 45

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
 50 55 60

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
 65 70 75 80

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
 85 90 95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
 100 105 110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
 115 120 125

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
 130 135 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
 145 150 155 160

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
 165 170 175

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Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
 180 185 190

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
 195 200 205

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
 210 215 220

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
 225 230 235 240

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 245 250

<210> 118
 <211> 252
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> TALL-1 inhibitory peptibodies

<400> 118

Met Asp Leu Asn Cys Lys Tyr Asp Glu Leu Thr Tyr Lys Glu Trp Cys
 1 5 10 15

Gln Phe Asn Gly Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro
 20 25 30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
 35 40 45

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
 50 55 60

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
 65 70 75 80

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
 85 90 95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
 100 105 110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
 115 120 125

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
 130 135 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
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145                               150                               155                               160

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
      165                               170                               175

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
      180                               185                               190

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
      195                               200                               205

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
      210                               215                               220

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
      225                               230                               235                               240

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
      245                               250

<210> 119
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<223> TALL-1 inhibitory peptibodies

<400> 119

Met Phe His Asp Cys Lys Tyr Asp Leu Leu Thr Arg Gln Met Val Cys
1      5      10      15

His Gly Leu Gly Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro
      20      25      30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
      35      40      45

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
      50      55      60

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
65      70      75      80

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
      85      90      95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
      100      105      110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
      115      120      125

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Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
 130 135 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
 145 150 155 160

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
 165 170 175

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
 180 185 190

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
 195 200 205

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
 210 215 220

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
 225 230 235 240

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 245 250

<210> 120

<211> 252

<212> PRT

<213> Artificial Sequence

<220>

<223> TALL-1 inhibitory peptibodies

<400> 120

Met Arg Asn His Cys Phe Trp Asp His Leu Leu Lys Gln Asp Ile Cys
 1 5 10 15

Pro Ser Pro Gly Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro
 20 25 30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
 35 40 45

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
 50 55 60

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
 65 70 75 80

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
 85 90 95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr

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100

105

110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
 115 120 125

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
 130 135 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
 145 150 155 160

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
 165 170 175

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
 180 185 190

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
 195 200 205

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
 210 215 220

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
 225 230 235 240

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 245 250

<210> 121

<211> 252

<212> PRT

<213> Artificial Sequence

<220>

<223> TALL-1 inhibitory peptibodies

<400> 121

Met Ala Asn Gln Cys Trp Trp Asp Ser Leu Thr Lys Lys Asn Val Cys
 1 5 10 15

Glu Phe Phe Gly Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro
 20 25 30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
 35 40 45

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
 50 55 60

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
 65 70 75 80

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Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
85 90 95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
100 105 110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
115 120 125

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
130 135 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
145 150 155 160

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
165 170 175

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
180 185 190

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
195 200 205

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
210 215 220

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
225 230 235 240

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
245 250

<210> 122

<211> 252

<212> PRT

<213> Artificial Sequence

<220>

<223> TALL 1 inhibitory peptibodies

<400> 122

Met Phe His Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Cys
1 5 10 15

His Gly Leu Gly Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro
20 25 30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
35 40 45

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
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60

50

55

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
65 70 75 80

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
85 90 95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
100 105 110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
115 120 125

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
130 135 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
145 150 155 160

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
165 170 175

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
180 185 190

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
195 200 205

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
210 215 220

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
225 230 235 240

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
245 250

<210> 123

<211> 293

<212> PRT

<213> Artificial Sequence

<220>

<223> TALL-1 inhibitory peptibodies

<400> 123

Met Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln Trp Val Cys
1 5 10 15

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

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Ser Ser Gly Ser Gly Ser Ala Thr His Met Leu Pro Gly Cys Lys Trp
 35 40 45
 Asp Leu Leu Ile Lys Gln Trp Val Cys Asp Pro Leu Gly Gly Gly Gly
 50 55 60
 Gly Val Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
 65 70 75 80
 Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
 85 90 95
 Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
 100 105 110
 Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
 115 120 125
 Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
 130 135 140
 Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
 145 150 155 160
 Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
 165 170 175
 Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
 180 185 190
 Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
 195 200 205
 Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
 210 215 220
 Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
 225 230 235 240
 Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
 245 250 255
 Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
 260 265 270
 Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
 275 280 285
 Leu Ser Pro Gly Lys
 290

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<210> 124
 <211> 293
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> TALL-1 inhibitory peptibodies

<400> 124

Met Phe His Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Cys
 1 5 10 15

His Gly Leu Gly Ser Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala
 20 25 30

Ser Ser Gly Ser Gly Ser Ala Thr His Met Phe His Asp Cys Lys Trp
 35 40 45

Asp Leu Leu Thr Lys Gln Trp Val Cys His Gly Leu Gly Gly Gly Gly
 50 55 60

Gly Val Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
 65 70 75 80

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
 85 90 95

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
 100 105 110

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
 115 120 125

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
 130 135 140

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
 145 150 155 160

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
 165 170 175

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
 180 185 190

Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
 195 200 205

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
 210 215 220

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
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225 230 235 240

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
 245 250 255

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
 260 265 270

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
 275 280 285

Leu Ser Pro Gly Lys
 290

<210> 125
 <211> 14
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Consensus Sequence

<220>
 <221> misc_feature
 <222> (1, 2 and)..(3)
 <223> X at (Pos 1, 2, 3) are absent or are amino acid residues (with on
 e of X1, X2, and X3 preferred to be C when one of X12,
 X13, and X14 is C);

<220>
 <221> misc_feature
 <222> (7)..(7)
 <223> X at (Pos 7) is an amino acid residue (L preferred);

<220>
 <221> misc_feature
 <222> (9)..(9)
 <223> X at (Pos 9) is T or I (T preferred);

<220>
 <221> misc_feature
 <222> (12)..(12)
 <223> X at (Pos 12) is C, a neutral hydrophobic residue, or a basic res
 idue (W, C, or R
 preferred);

<220>
 <221> misc_feature
 <222> (13)..(13)
 <223> X at (Pos 13) is C, a neutral hydrophobic residue or is absent (V
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preferred);

<220>
 <221> misc_feature
 <222> (14)..(14)
 <223> X at (Pos 14) is any amino acid residue or is absent.

<400> 125

Xaa Xaa Xaa Lys Trp Asp Xaa Leu Xaa Lys Gln Xaa Xaa Xaa
 1 5 10

<210> 126
 <211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Preferred TALL-1 modulating domains

<400> 126

Tyr Lys Gly Arg Gln Met Trp Asp Ile Leu Thr Arg Ser Trp Val Val
 1 5 10 15

Ser Leu

<210> 127
 <211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Preferred TALL-1 modulating domains

<400> 127

Gln Asp Val Gly Leu Trp Trp Asp Ile Leu Thr Arg Ala Trp Met Pro
 1 5 10 15

Asn Ile

<210> 128
 <211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Preferred TALL-1 modulating domains

<400> 128

Gln Asn Ala Gln Arg Val Trp Asp Leu Leu Ile Arg Thr Trp Val Tyr
 1 5 10 15

Pro Gln

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<210> 129
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 129

Gly Trp Asn Glu Ala Trp Trp Asp Glu Leu Thr Lys Ile Trp Val Leu
1 5 10 15

Glu Gln

<210> 130
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 130

Arg Ile Thr Cys Asp Thr Trp Asp Ser Leu Ile Lys Lys Cys Val Pro
1 5 10 15

Gln Ser

<210> 131
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 131

Gly Ala Ile Met Gln Phe Trp Asp Ser Leu Thr Lys Thr Trp Leu Arg
1 5 10 15

Gln Ser

<210> 132
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 132

Trp Leu His Ser Gly Trp Trp Asp Pro Leu Thr Lys His Trp Leu Gln
1 5 10 15

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Lys Val

<210> 133
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 133

Ser	Glu	Trp	Phe	Phe	Trp	Phe	Asp	Pro	Leu	Thr	Arg	Ala	Gln	Leu	Lys
1				5					10					15	

Phe Arg

<210> 134
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 134

Gly	Val	Trp	Phe	Trp	Trp	Phe	Asp	Pro	Leu	Thr	Lys	Gln	Trp	Thr	Gln
1				5					10					15	

Ala Gly

<210> 135
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 135

Met	Gln	Cys	Lys	Gly	Tyr	Tyr	Asp	Ile	Leu	Thr	Lys	Trp	Cys	Val	Thr
1				5					10					15	

Asn Gly

<210> 136
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 136

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Leu Trp Ser Lys Glu Val Trp Asp Ile Leu Thr Lys Ser Trp Val Ser
 1 5 10 15

Gln Ala

<210> 137
 <211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Preferred TALL-1 modulating domains

<400> 137

Lys Ala Ala Gly Trp Trp Phe Asp Trp Leu Thr Lys Val Trp Val Pro
 1 5 10 15

Ala Pro

<210> 138
 <211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Preferred TALL-1 modulating domains

<400> 138

Ala Tyr Gln Thr Trp Phe Trp Asp Ser Leu Thr Arg Leu Trp Leu Ser
 1 5 10 15

Thr Thr

<210> 139
 <211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Preferred TALL-1 modulating domains

<400> 139

Ser Gly Gln His Phe Trp Trp Asp Leu Leu Thr Arg Ser Trp Thr Pro
 1 5 10 15

Ser Thr

<210> 140
 <211> 18
 <212> PRT
 <213> Artificial Sequence

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<220>

<223> Preferred TALL-1 modulating domains

<400> 140

Leu Gly Val Gly Gln Lys Trp Asp Pro Leu Thr Lys Gln Trp Val Ser
1 5 10 15

Arg Gly

<210> 141

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Preferred TALL-1 modulating domains

<400> 141

Val Gly Lys Met Cys Gln Trp Asp Pro Leu Ile Lys Arg Thr Val Cys
1 5 10 15

Val Gly

<210> 142

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Preferred TALL-1 modulating domains

<400> 142

Cys Arg Gln Gly Ala Lys Phe Asp Leu Leu Thr Lys Gln Cys Leu Leu
1 5 10 15

Gly Arg

<210> 143

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Preferred TALL-1 modulating domains

<400> 143

Gly Gln Ala Ile Arg His Trp Asp Val Leu Thr Lys Gln Trp Val Asp
1 5 10 15

Ser Gln

<210> 144

A-743 PCT.ST25.txt

<211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Preferred TALL-1 modulating domains

<400> 144

Arg	Gly	Pro	Cys	Gly	Ser	Trp	Asp	Leu	Leu	Thr	Lys	His	Cys	Leu	Asp
1				5					10					15	

Ser Gln

<210> 145
 <211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Preferred TALL-1 modulating domains

<400> 145

Trp	Gln	Trp	Lys	Gln	Gln	Trp	Asp	Leu	Leu	Thr	Lys	Gln	Met	Val	Trp
1				5					10					15	

Val Gly

<210> 146
 <211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Preferred TALL-1 modulating domains

<400> 146

Pro	Ile	Thr	Ile	Cys	Arg	Lys	Asp	Leu	Leu	Thr	Lys	Gln	Val	Val	Cys
1				5					10					15	

Leu Asp

<210> 147
 <211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Preferred TALL-1 modulating domains

<400> 147

Lys	Thr	Cys	Asn	Gly	Lys	Trp	Asp	Leu	Leu	Thr	Lys	Gln	Cys	Leu	Gln
1				5					10					15	

Gln Ala

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<210> 148
 <211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Preferred TALL-1 modulating domains

<400> 148

Lys Cys Leu Lys Gly Lys Trp Asp Leu Leu Thr Lys Gln Cys Val Thr
 1 5 10 15

Glu Val

<210> 149
 <211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Preferred TALL-1 modulating domains

<400> 149

Arg Cys Trp Asn Gly Lys Trp Asp Leu Leu Thr Lys Gln Cys Ile His
 1 5 10 15

Pro Trp

<210> 150
 <211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Preferred TALL-1 modulating domains

<400> 150

Asn Arg Asp Met Arg Lys Trp Asp Pro Leu Ile Lys Gln Trp Ile Val
 1 5 10 15

Arg Pro

<210> 151
 <211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Preferred TALL-1 modulating domains

<400> 151

Gln Ala Ala Ala Ala Thr Trp Asp Leu Leu Thr Lys Gln Trp Leu Val
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1 5 10 15

Pro Pro

<210> 152
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 152

Pro Glu Gly Gly Pro Lys Trp Asp Pro Leu Thr Lys Gln Phe Leu Pro
1 5 10 15

Pro Val

<210> 153
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 153

Gln Thr Pro Gln Lys Lys Trp Asp Leu Leu Thr Lys Gln Trp Phe Thr
1 5 10 15

Arg Asn

<210> 154
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 154

Ile Gly Ser Pro Cys Lys Trp Asp Leu Leu Thr Lys Gln Met Ile Cys
1 5 10 15

Gln Thr

<210> 155
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

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<400> 155

Cys Thr Ala Ala Gly Lys Trp Asp Leu Leu Thr Lys Gln Cys Ile Gln
1 5 10 15

Glu Lys

<210> 156

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Preferred TALL-1 modulating domains

<400> 156

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

Gly Trp

<210> 157

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Preferred TALL-1 modulating domains

<400> 157

Val Trp Gly Thr Trp Lys Trp Asp Leu Leu Thr Lys Gln Tyr Leu Pro
1 5 10 15

Pro Gln

<210> 158

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Preferred TALL-1 modulating domains

<400> 158

Gly Trp Trp Glu Met Lys Trp Asp Leu Leu Thr Lys Gln Trp Tyr Arg
1 5 10 15

Pro Gln

<210> 159

<211> 18

<212> PRT

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<213> Artificial Sequence

<220>

<223> Preferred TALL-1 modulating domains

<400> 159

Thr	Ala	Gln	Val	Ser	Lys	Trp	Asp	Leu	Leu	Thr	Lys	Gln	Trp	Leu	Pro
1				5				10						15	

Leu Ala

<210> 160

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Preferred TALL-1 modulating domains

<400> 160

Gln	Leu	Trp	Gly	Thr	Lys	Trp	Asp	Leu	Leu	Thr	Lys	Gln	Tyr	Ile	Gln
1				5				10						15	

Ile Met

<210> 161

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Preferred TALL-1 modulating domains

<400> 161

Trp	Ala	Thr	Ser	Gln	Lys	Trp	Asp	Leu	Leu	Thr	Lys	Gln	Trp	Val	Gln
1				5				10						15	

Asn Met

<210> 162

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Preferred TALL-1 modulating domains

<400> 162

Gln	Arg	Gln	Cys	Ala	Lys	Trp	Asp	Leu	Leu	Thr	Lys	Gln	Cys	Val	Leu
1				5				10						15	

Phe Tyr

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<210> 163
 <211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Preferred TALL-1 modulating domains

<400> 163

Lys Thr Thr Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln Arg Ile Cys
 1 5 10 15

Gln Val

<210> 164
 <211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Preferred TALL-1 modulating domains

<400> 164

Leu Leu Cys Gln Gly Lys Trp Asp Leu Leu Thr Lys Gln Cys Leu Lys
 1 5 10 15

Leu Arg

<210> 165
 <211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Preferred TALL-1 modulating domains

<400> 165

Leu Met Trp Phe Trp Lys Trp Asp Leu Leu Thr Lys Gln Leu Val Pro
 1 5 10 15

Thr Phe

<210> 166
 <211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Preferred TALL-1 modulating domains

<400> 166

Gln Thr Trp Ala Trp Lys Trp Asp Leu Leu Thr Lys Gln Trp Ile Gly
 1 5 10 15

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Pro Met

<210> 167
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 167

Asn	Lys	Glu	Leu	Leu	Lys	Trp	Asp	Leu	Leu	Thr	Lys	Gln	Cys	Arg	Gly
1			5						10					15	

Arg Ser

<210> 168
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 168

Gly	Gln	Lys	Asp	Leu	Lys	Trp	Asp	Leu	Leu	Thr	Lys	Gln	Tyr	Val	Arg
1				5					10					15	

Gln Ser

<210> 169
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 169

Pro	Lys	Pro	Cys	Gln	Lys	Trp	Asp	Leu	Leu	Thr	Lys	Gln	Cys	Leu	Gly
1				5					10					15	

Ser Val

<210> 170
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 170

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Gly Gln Ile Gly Trp Lys Trp Asp Leu Leu Thr Lys Gln Trp Ile Gln
 1 5 10 15

Thr Arg

<210> 171
 <211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Preferred TALL-1 modulating domains

<400> 171

Val Trp Leu Asp Trp Lys Trp Asp Leu Leu Thr Lys Gln Trp Ile His
 1 5 10 15

Pro Gln

<210> 172
 <211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Preferred TALL-1 modulating domains

<400> 172

Gln Glu Trp Glu Tyr Lys Trp Asp Leu Leu Thr Lys Gln Trp Gly Trp
 1 5 10 15

Leu Arg

<210> 173
 <211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Preferred TALL-1 modulating domains

<400> 173

His Trp Asp Ser Trp Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Val
 1 5 10 15

Gln Ala

<210> 174
 <211> 18
 <212> PRT
 <213> Artificial Sequence

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<220>

<223> Preferred TALL-1 modulating domains

<400> 174

Thr	Arg	Pro	Leu	Gln	Lys	Trp	Asp	Leu	Leu	Thr	Lys	Gln	Trp	Leu	Arg
1				5					10					15	

Val Gly

<210> 175

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Preferred TALL-1 modulating domains

<400> 175

Ser	Asp	Gln	Trp	Gln	Lys	Trp	Asp	Leu	Leu	Thr	Lys	Gln	Trp	Phe	Trp
1				5					10					15	

Asp Val

<210> 176

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Preferred TALL-1 modulating domains

<400> 176

Gln	Gln	Thr	Phe	Met	Lys	Trp	Asp	Leu	Leu	Thr	Lys	Gln	Trp	Ile	Arg
1				5					10					15	

Arg His

<210> 177

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Preferred TALL-1 modulating domains

<400> 177

Gln	Gly	Glu	Cys	Arg	Lys	Trp	Asp	Leu	Leu	Thr	Lys	Gln	Cys	Phe	Pro
1				5					10					15	

Gly Gln

<210> 178

A-743 PCT.ST25.txt

<211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Preferred TALL-1 modulating domains

<400> 178

Gly Gln Met Gly Trp Arg Trp Asp Pro Leu Ile Lys Met Cys Leu Gly
 1 5 10 15

Pro Ser

<210> 179
 <211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Preferred TALL-1 modulating domains

<400> 179

Gln Leu Asp Gly Cys Lys Trp Asp Leu Leu Thr Lys Gln Lys Val Cys
 1 5 10 15

Ile Pro

<210> 180
 <211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Preferred TALL-1 modulating domains

<400> 180

His Gly Tyr Trp Gln Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Ser
 1 5 10 15

Ser Glu

<210> 181
 <211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Preferred TALL-1 modulating domains

<400> 181

His Gln Gly Gln Cys Gly Trp Asp Leu Leu Thr Arg Ile Tyr Leu Pro
 1 5 10 15

Cys His

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<210> 182
 <211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Preferred TALL-1 modulating domains

<400> 182

Leu His Lys Ala Cys Lys Trp Asp Leu Leu Thr Lys Gln Cys Trp Pro
 1 5 10 15

Met Gln

<210> 183
 <211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Preferred TALL-1 modulating domains

<400> 183

Gly Pro Pro Gly Ser Val Trp Asp Leu Leu Thr Lys Ile Trp Ile Gln
 1 5 10 15

Thr Gly

<210> 184
 <211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Preferred TALL-1 modulating domains

<400> 184

Ile Thr Gln Asp Trp Arg Phe Asp Thr Leu Thr Arg Leu Trp Leu Pro
 1 5 10 15

Leu Arg

<210> 185
 <211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Preferred TALL-1 modulating domains

<400> 185

Gln Gly Gly Phe Ala Ala Trp Asp Val Leu Thr Lys Met Trp Ile Thr
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10

1 5 15

Val Pro

<210> 186
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 186

Gly His Gly Thr Pro Trp Trp Asp Ala Leu Thr Arg Ile Trp Ile Leu
1 5 10 15

Gly Val

<210> 187
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 187

Val Trp Pro Trp Gln Lys Trp Asp Leu Leu Thr Lys Gln Phe Val Phe
1 5 10 15

Gln Asp

<210> 188
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 188

Trp Gln Gln Trp Ser Trp Lys Trp Asp Leu Leu Thr Arg Gln Tyr Ile
1 5 10 15

Ser Ser Ser

<210> 189
<211> 882
<212> DNA
<213> Artificial Sequence

<220>
<223> TALL-1 12-3 tandem dimer

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<400> 189
atgcttccag gctgcaagtg ggatcttctt attaagcaat gggatatgca tccacttgga      60
tccggttctg ctactggtgg ttccggctcc accgcaagct ctgggttcagg cagtgcgact      120
catatgctgc cgggttgtaa atgggacctg ctgatcaaac agtggggttg tgacccgctg      180
ggtggaggcg gtggggtcga caaaactcac acatgtccac cttgtccagc tccggaactc      240
ctgggggggac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc      300
cggacccctg aggtcacatg cgtgggtggtg gacgtgagcc acgaagaccc tgagggtcaag      360
ttcaactggt acgtggacgg cgtggagggtg cataatgcca agacaaagcc gcgggaggag      420
cagtacaaca gcacgtaccg tgtgggtcagc gtcctcaccg tcctgcacca ggactggctg      480
aatggcaagg agtacaagtg caaggtctcc aacaaagccc tcccagcccc catcgagaaa      540
accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gccccatcc      600
cgggatgagc tgaccaagaa ccaggtcagc ctgacctgcc tgggtcaaagg cttctatccc      660
agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg      720
cctcccgtgc tggactccga cggctccttc ttctctaca gcaagctcac cgtggacaag      780
agcagggtggc agcaggggaa cgtcttctca tgctccgtga tgcattgaggc tctgcacaac      840
cactacacgc agaagagcct ctccctgtct ccgggtaaat aa                        882

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<210> 190
<211> 23
<212> PRT
<213> Artificial Sequence

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<220>
<223> Preferred linker

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<400> 190

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Gly Ser Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser Ser Gly
1           5           10          15

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Ser Gly Ser Ala Thr Gly Met
                20

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<210> 191
<211> 23
<212> PRT
<213> Artificial Sequence

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<220>
<223> Preferred linker

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<400> 191

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Gly Ser Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser Ser Gly
1           5           10          15

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Ser Gly Ser Ala Thr Gly Ser
                20

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Ser Gly Ser Ala Thr Xaa Xaa Gly Ser Gly Ser Ala Thr Gly Gly Ser
 20 25 30

Gly Ser Thr Ala Ser Ser Gly Ser Gly Ser Ala Thr Xaa Xaa
 35 40 45

<210> 195
 <211> 38
 <212> PRT
 <213> Human

<400> 195

Met Arg Arg Gly Pro Arg Ser Leu Arg Gly Arg Asp Ala Pro Val Pro
 1 5 10 15

Thr Pro Cys Val Pro Thr Glu Cys Tyr Asp Leu Leu Val Arg Lys Cys
 20 25 30

Val Asp Cys Arg Leu Leu
 35

<210> 196
 <211> 41
 <212> PRT
 <213> Human

<400> 196

Thr Ile Cys Asn His Gln Ser Gln Arg Thr Cys Ala Ala Phe Cys Arg
 1 5 10 15

Ser Leu Ser Cys Arg Lys Glu Gln Gly Lys Phe Tyr Asp His Leu Leu
 20 25 30

Arg Asp Cys Ile Ser Cys Ala Ser Ile
 35 40

<210> 197
 <211> 42
 <212> PRT
 <213> Human

<400> 197

Phe Val Ser Pro Ser Gln Glu Ile Arg Gly Arg Phe Arg Arg Met Leu
 1 5 10 15

Gln Met Ala Gly Gln Cys Ser Gln Asn Glu Tyr Phe Asp Ser Leu Leu
 20 25 30

His Ala Cys Ile Pro Cys Gln Leu Arg Cys
 35 40