



US 20150218280A1

(19) **United States**(12) **Patent Application Publication**
Epstein et al.(10) **Pub. No.: US 2015/0218280 A1**(43) **Pub. Date: Aug. 6, 2015**(54) **CD20 SCFV-ELPS METHODS AND
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§ 371 (c)(1),

(2) Date: **Feb. 6, 2015****Related U.S. Application Data**(60) Provisional application No. 61/682,029, filed on Aug.
10, 2012.**Publication Classification**(51) **Int. Cl.****C07K 16/28** (2006.01)**C07K 14/78** (2006.01)**A61K 47/48** (2006.01)(52) **U.S. Cl.**CPC **C07K 16/2887** (2013.01); **A61K 47/48561**
(2013.01); **C07K 14/78** (2013.01); **C07K**
2319/33 (2013.01)

(57)

ABSTRACTDisclosed herein are recombinant polypeptides comprising
an elastin-like peptide (ELP) and a scFv, or a biological
equivalent of the scFv. Also disclosed are compositions con-
taining scFv-ELP polypeptides and methods of use.

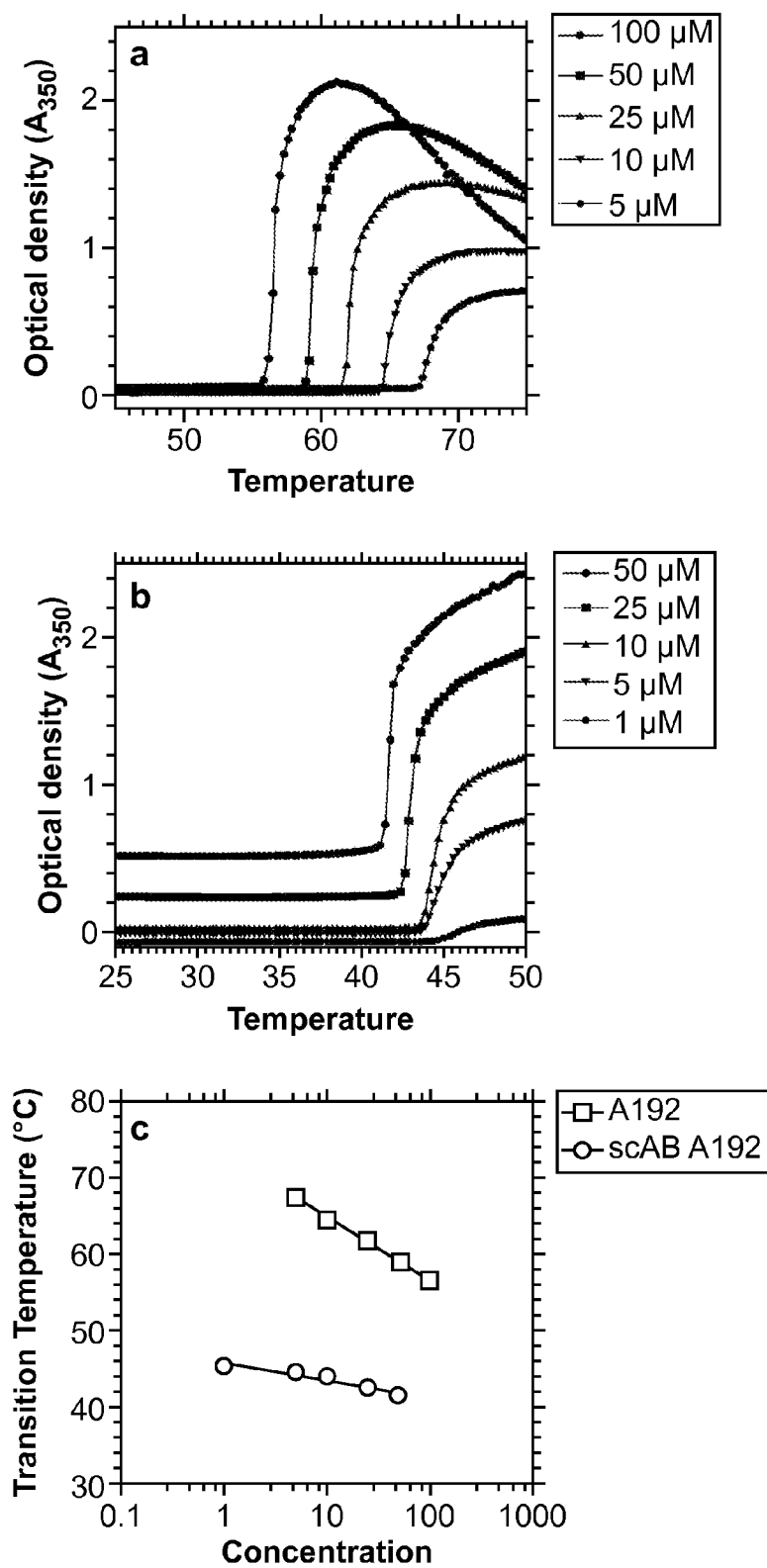


FIG. 1

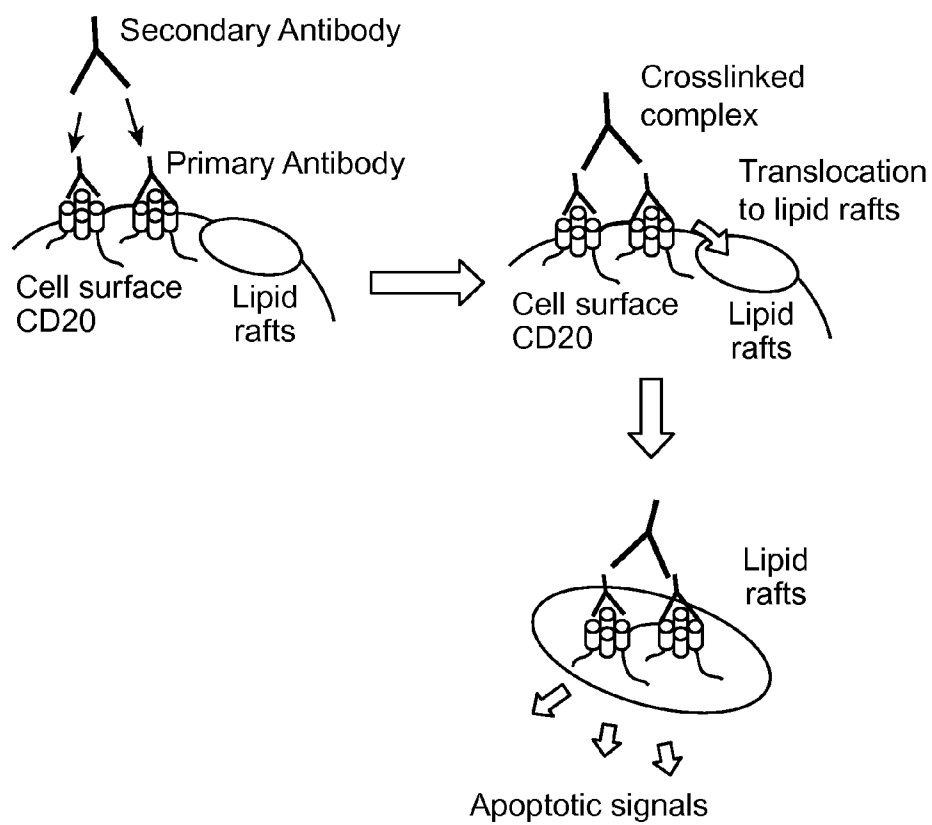


FIG. 2

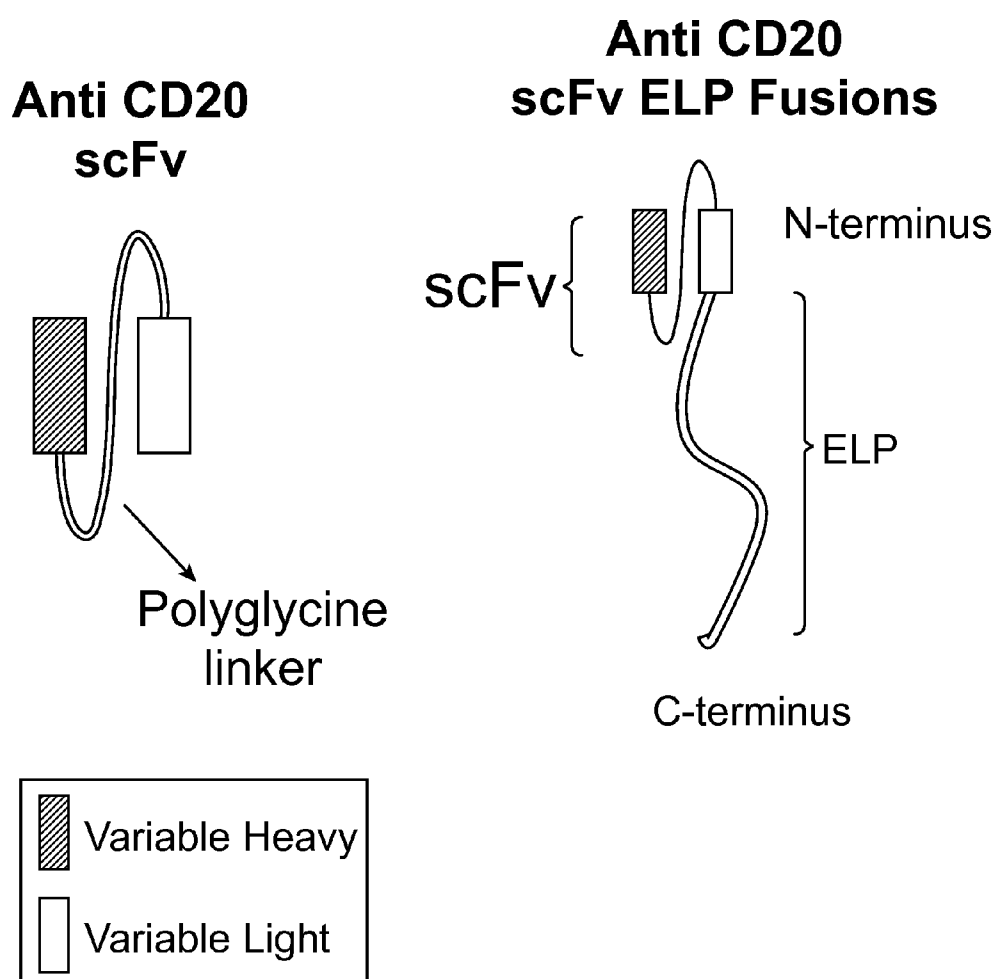


FIG. 3

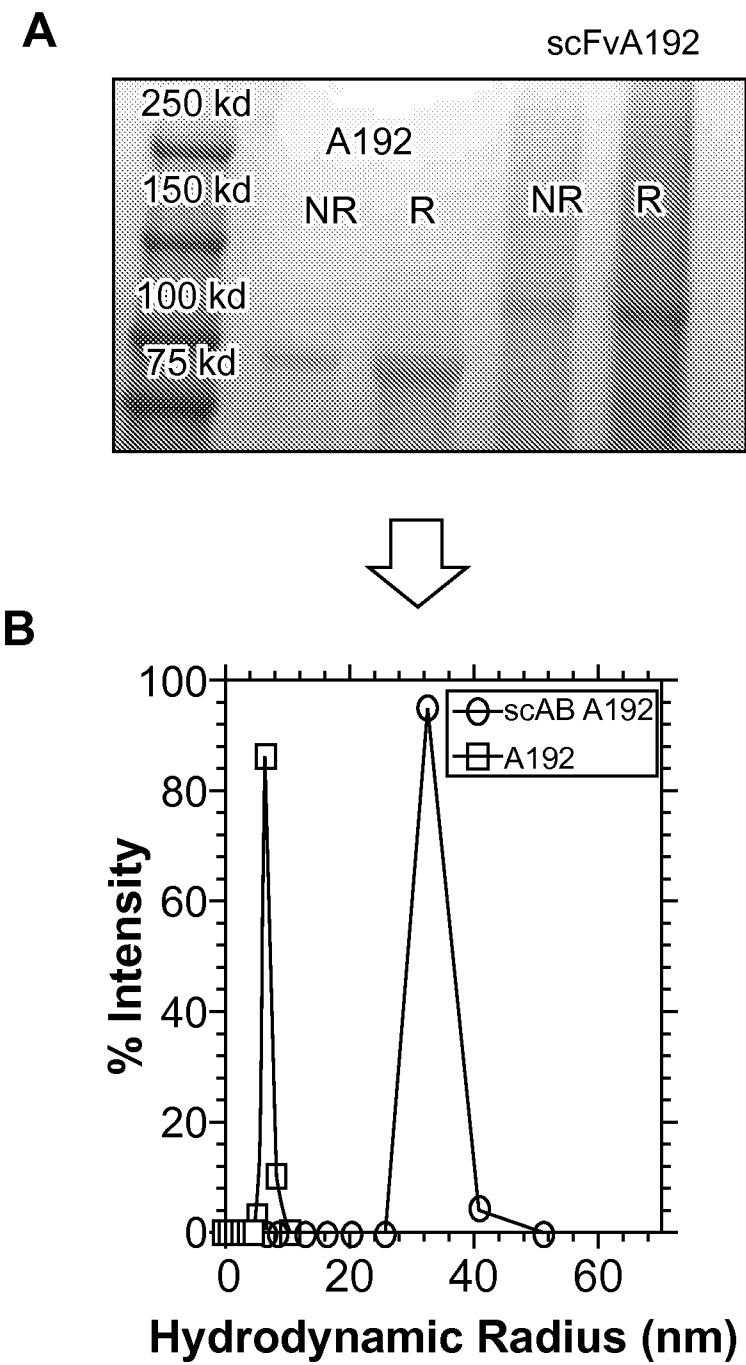


FIG. 4

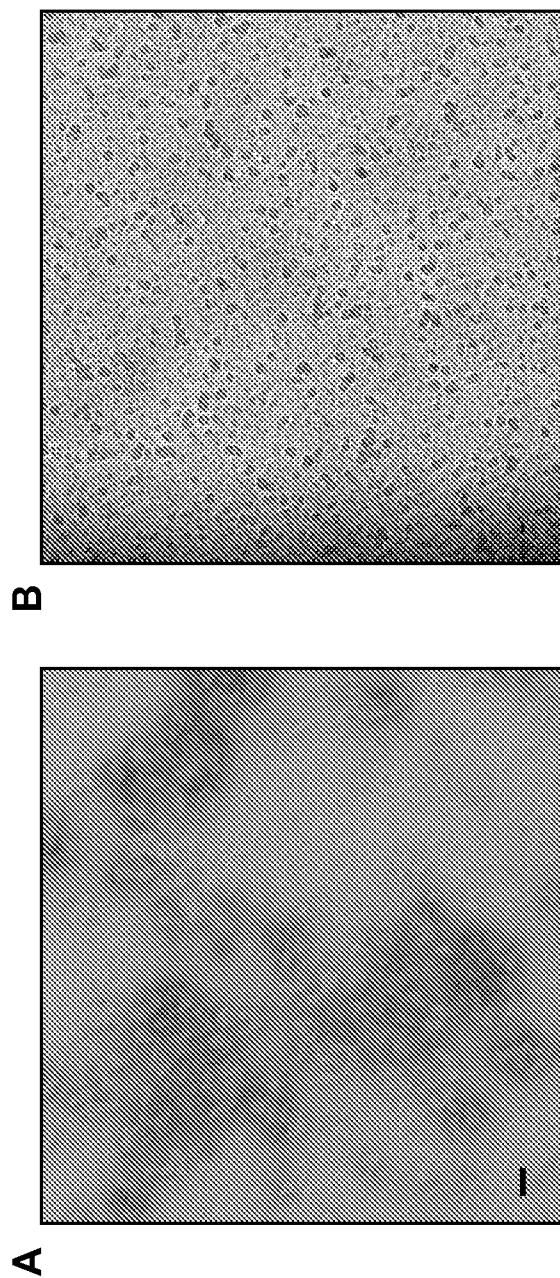


FIG. 5

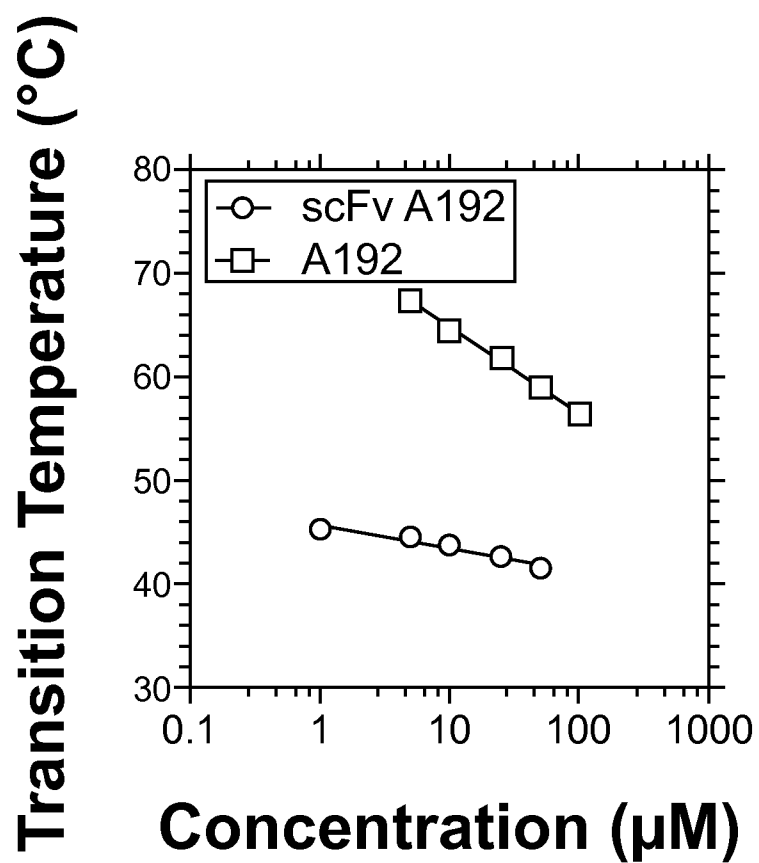


FIG. 6

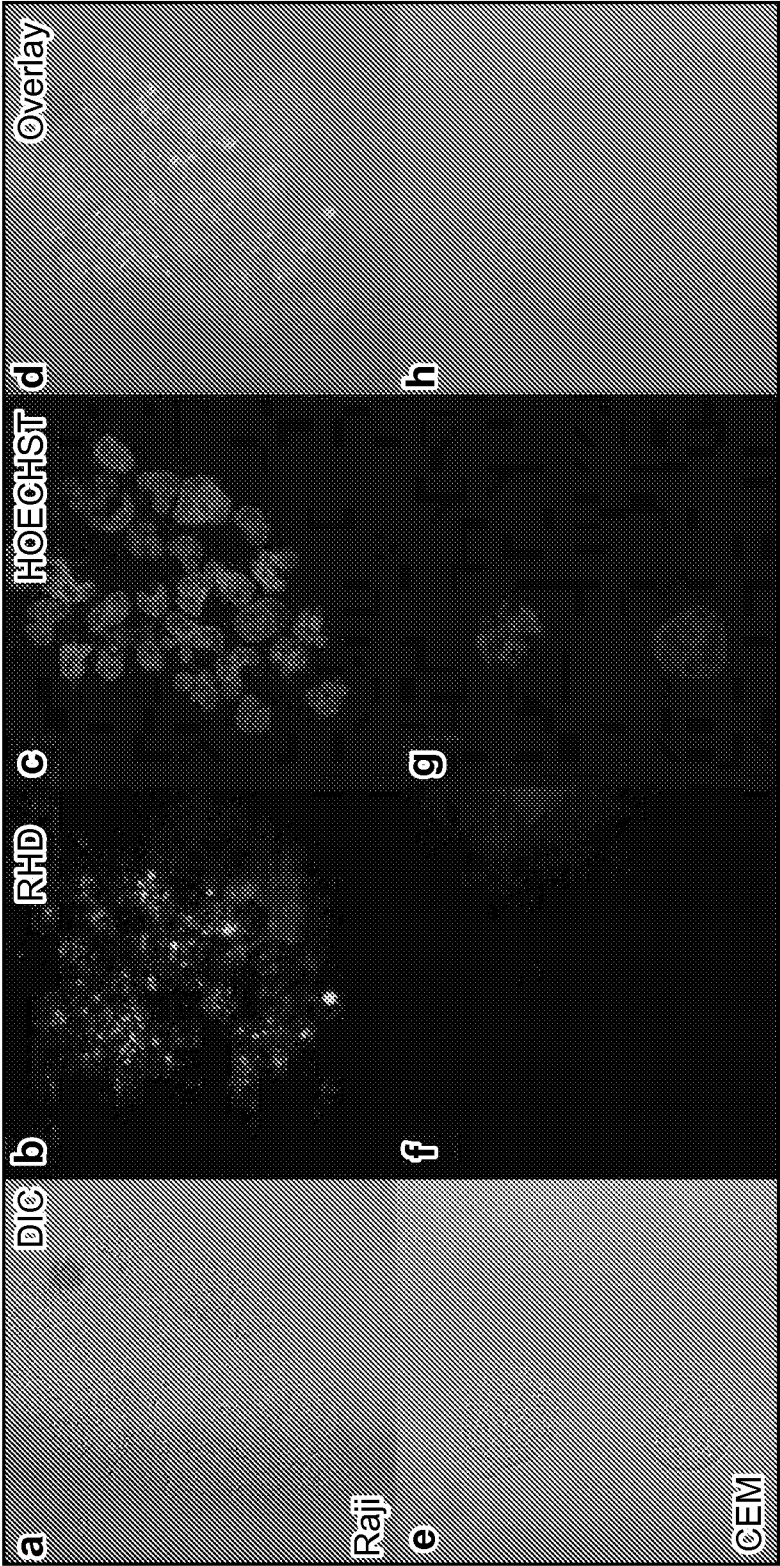


FIG. 7

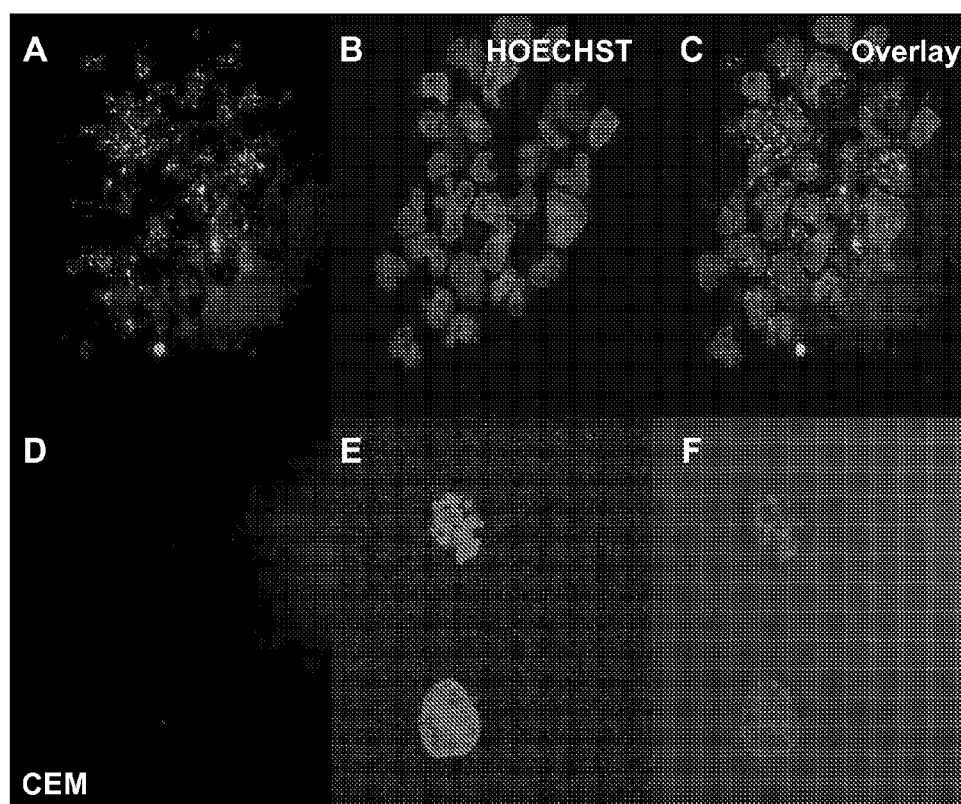


FIG. 8

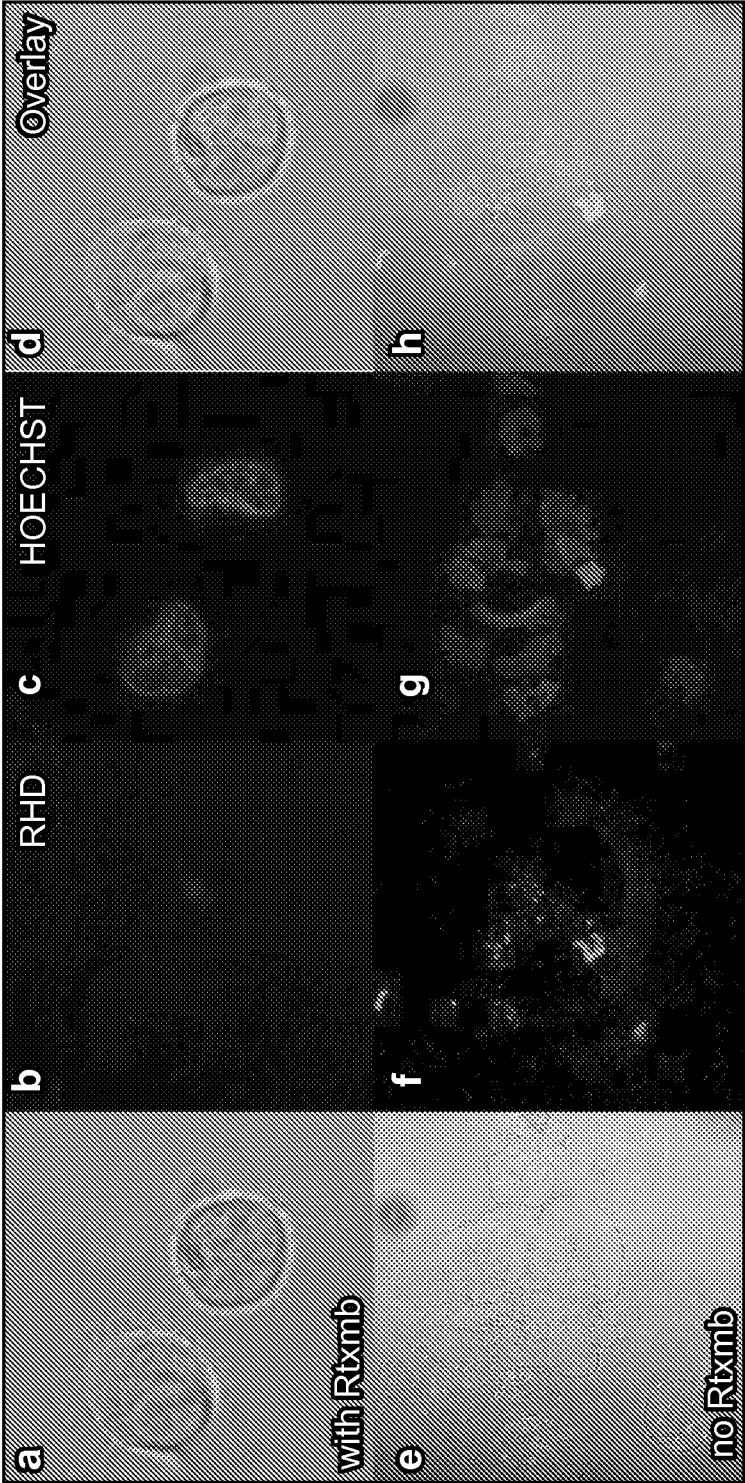


FIG. 9

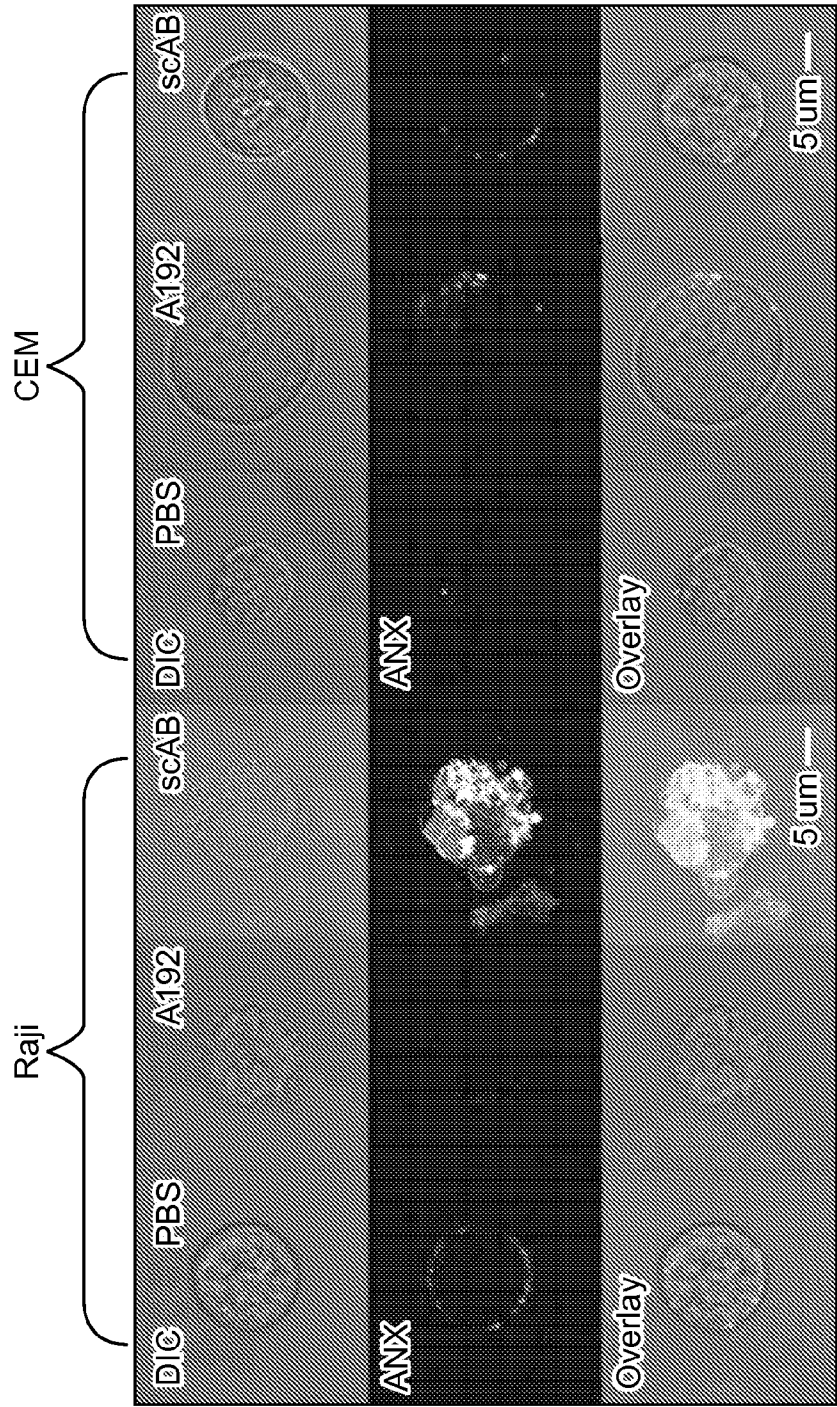


FIG. 10

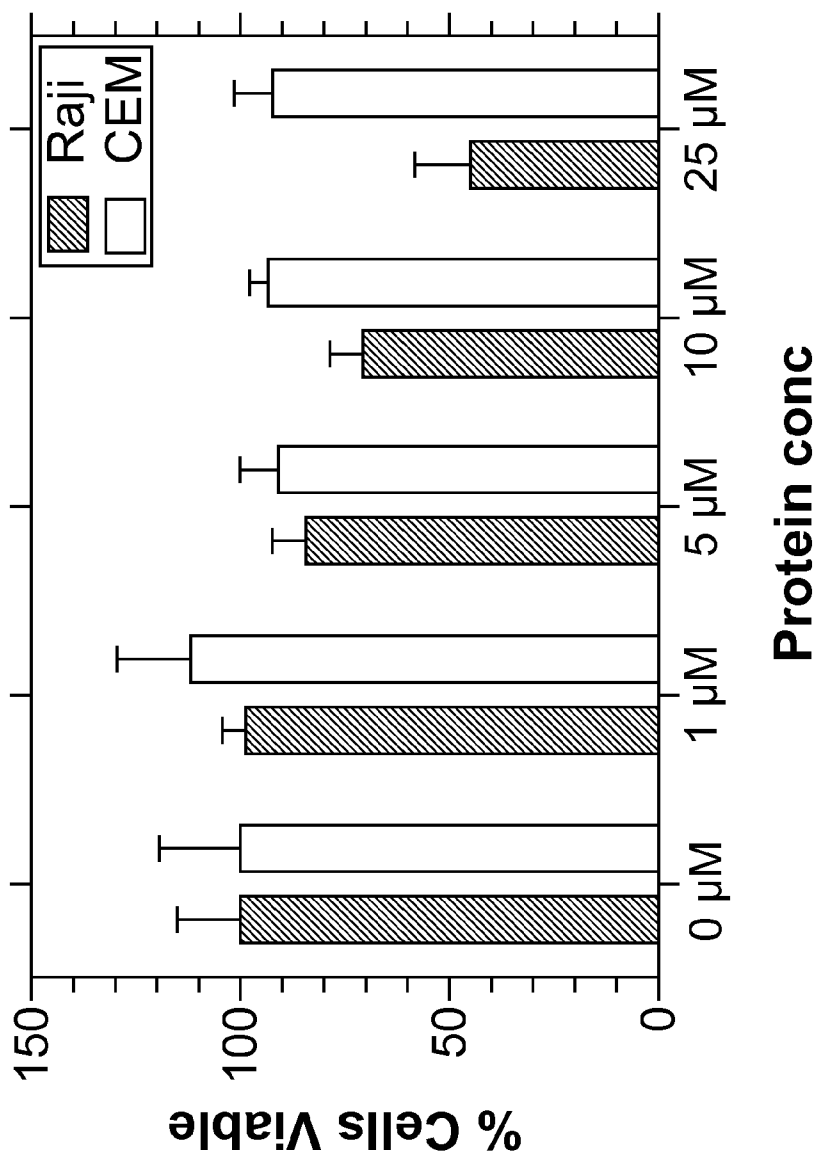


FIG. 11

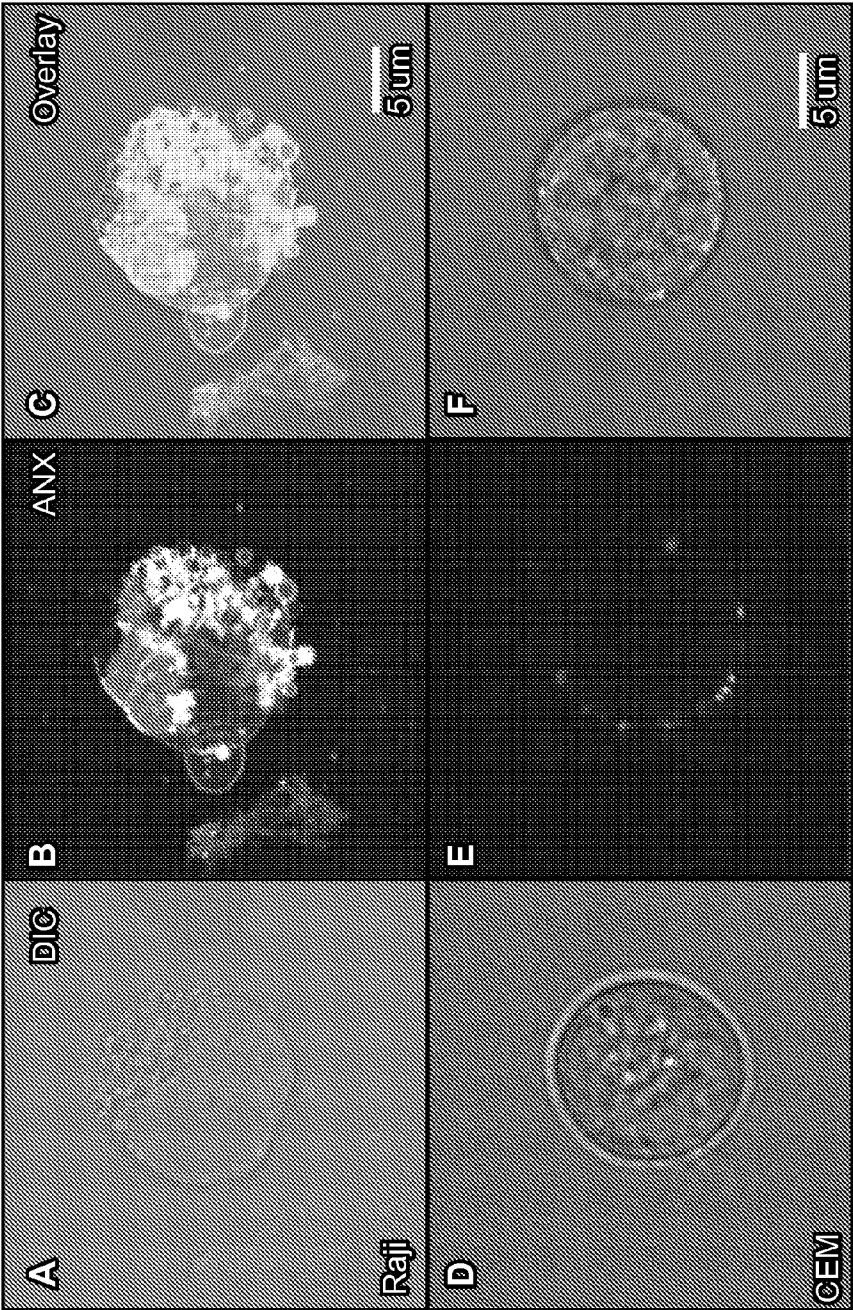
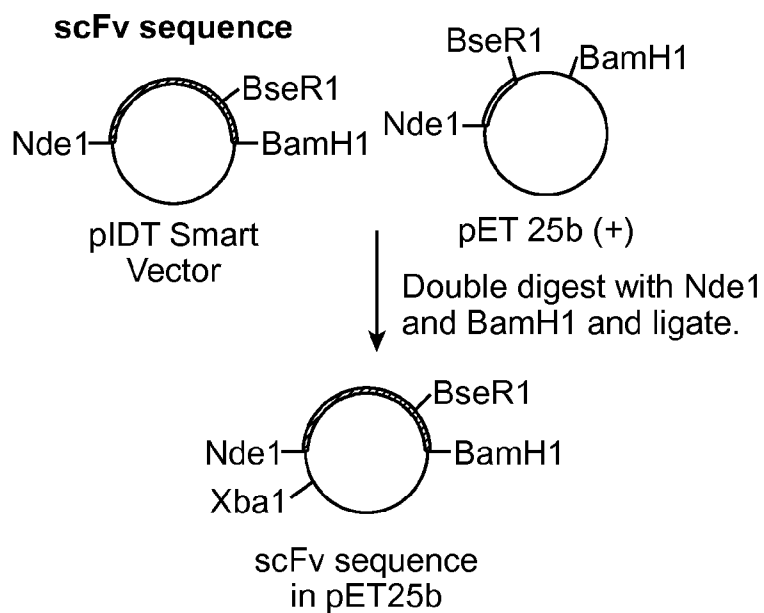


FIG. 12

Step 1:



Step 2:

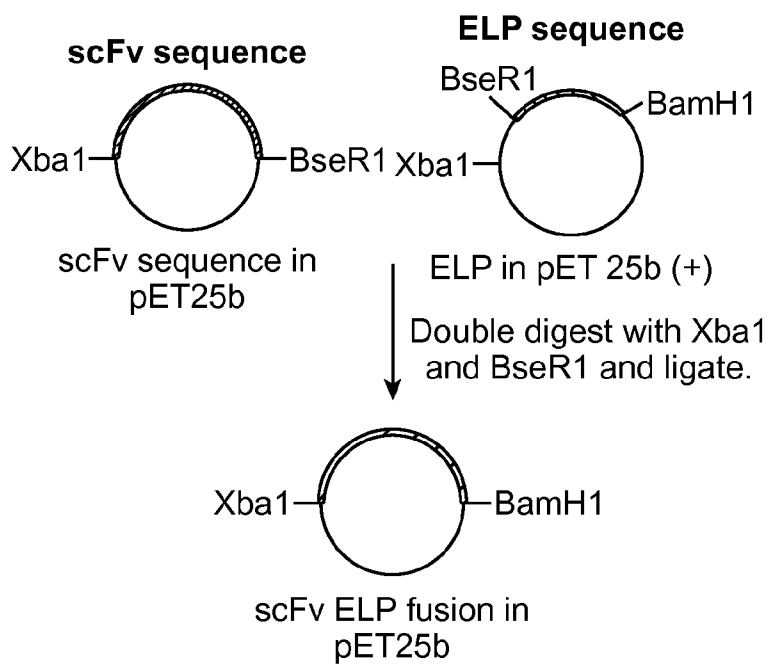


FIG. 13

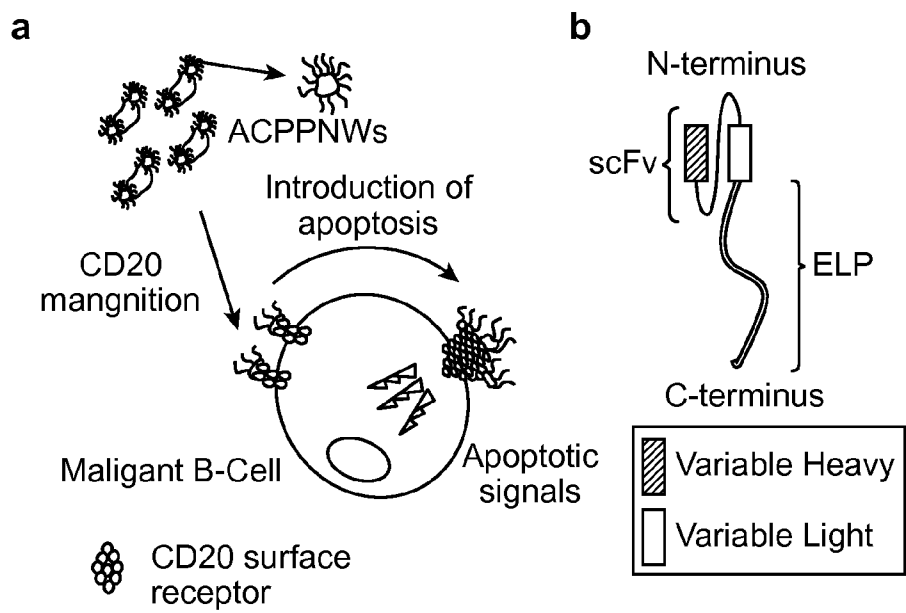


FIG. 14

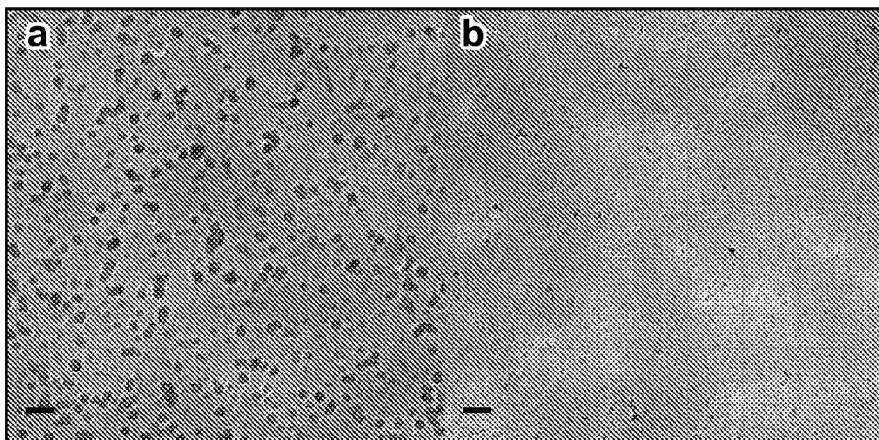


FIG. 15

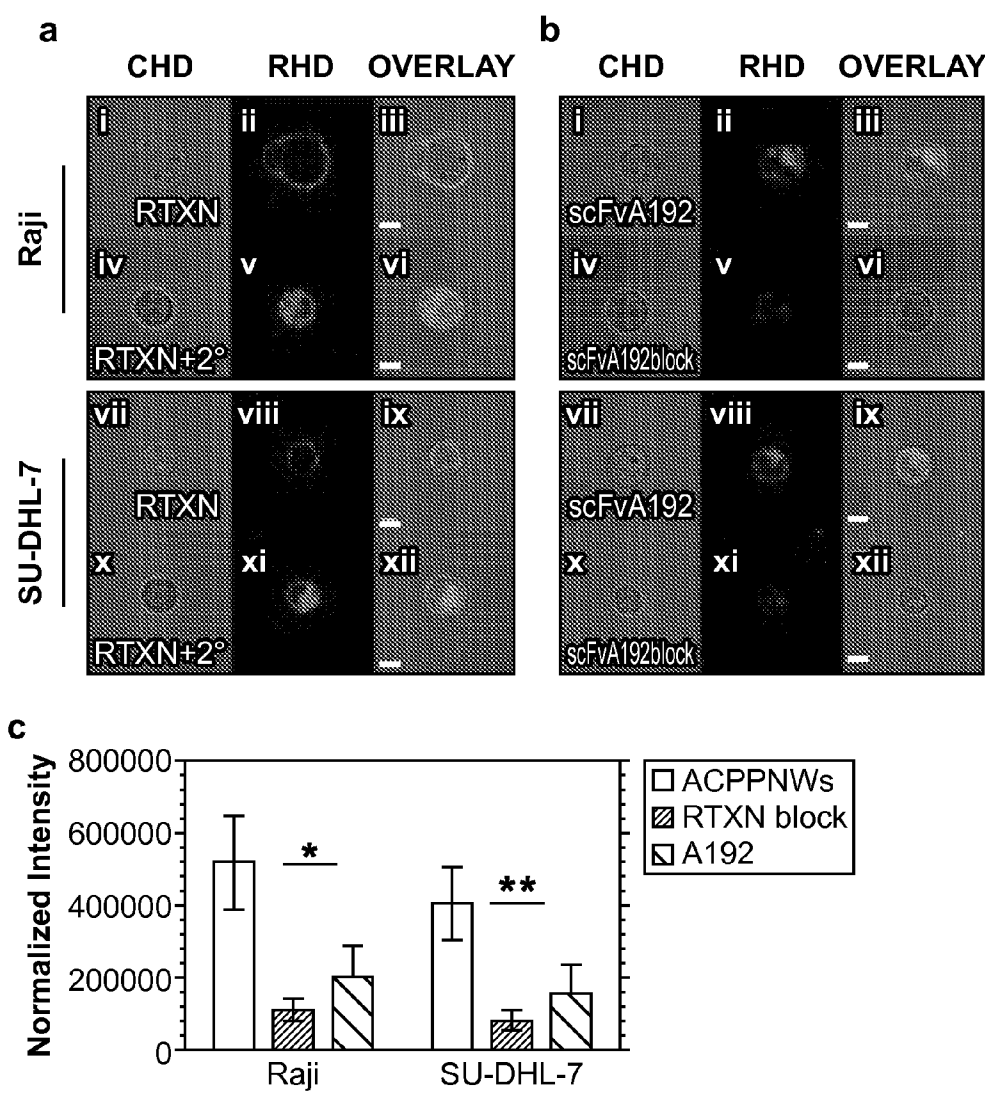


FIG. 16

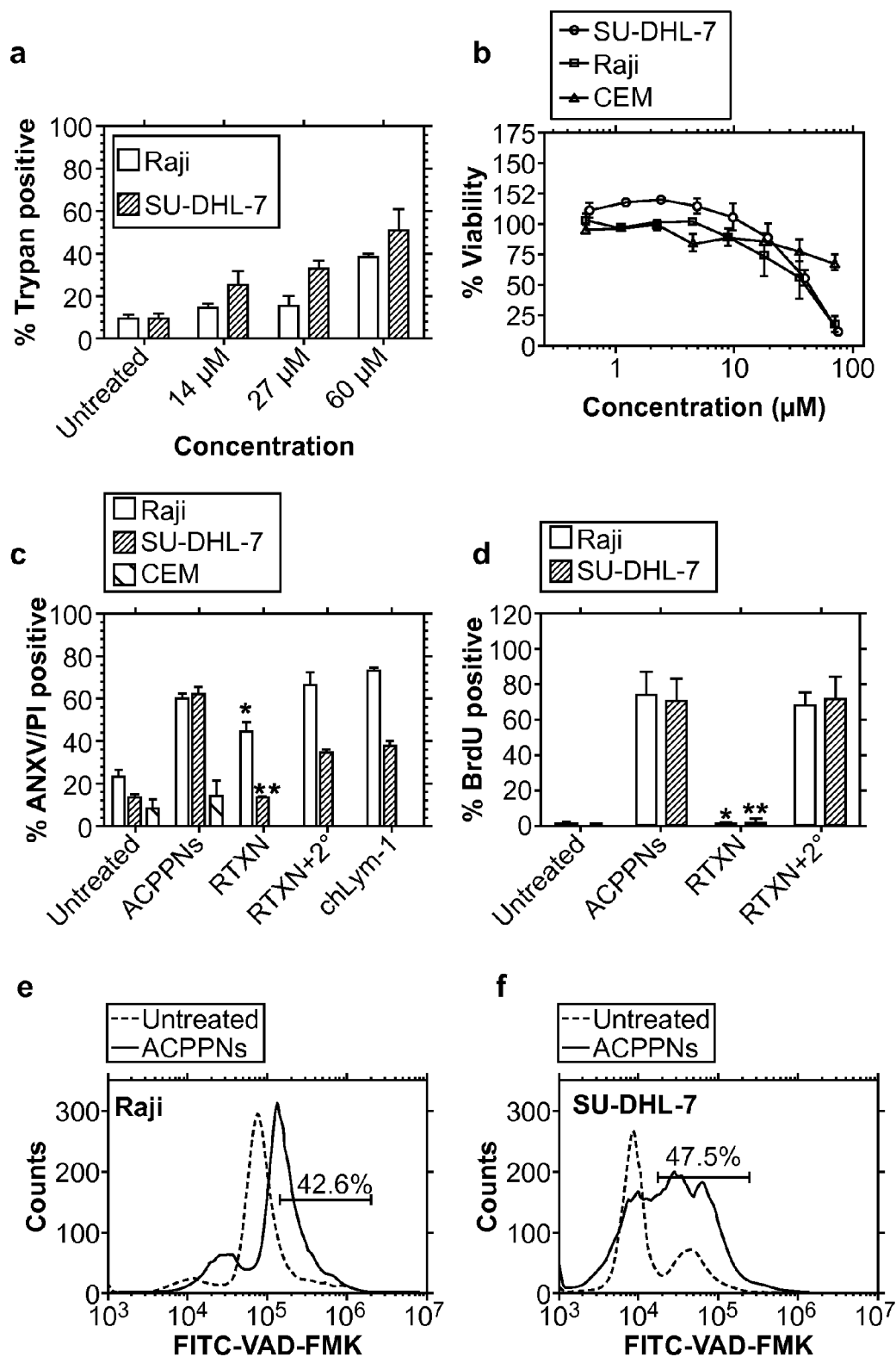


FIG. 17

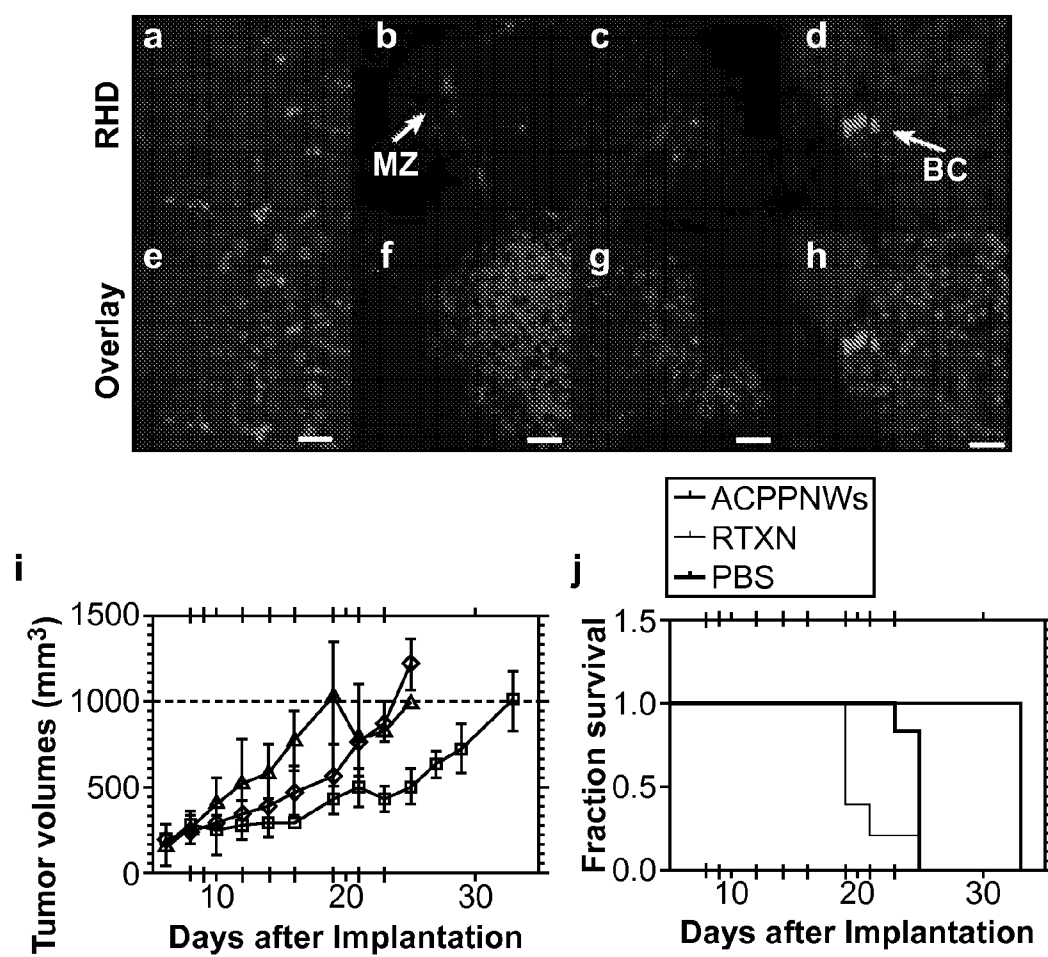


FIG. 18

CD20 SCFV-ELPS METHODS AND THERAPEUTICS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit under 35 U.S.C. §119(e) of U.S. Provisional Application Ser. No. 61/682,029, filed Aug. 10, 2012, the content of which is incorporated by reference into the present disclosure in its entirety.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety. Said ASCII copy, created on Aug. 8, 2013, is named 075405-1860_SL.txt and is 223,372 bytes in size.

BACKGROUND

[0003] Non-Hodgkin Lymphoma (NHL) accounts for 4% of all reported cancers. The most prescribed course of treatment is a regimen of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP). The CHOP regimen, developed in the 70's, is effective in 90% of the patients but is responsible for severe side effects.

[0004] NHL is characterized by increased production of malignant B-cells, which can be targeted specifically through cell-surface CD20. Antibodies against CD20 have been developed for NHL and have successfully made their way to the clinic. The most prominent example is Rituximab™, a chimeric antibody that targets malignant as well as normal B-cells. Crosslinking of Rituximab™ using a secondary antibody against the Fc region promotes cell apoptosis, which led to the observation that CD20-mediated apoptosis can be potentiated through strategies that induce multivalency. Multivalent antibodies against CD20 are potent inhibitors of the MAP Kinase pathway and upregulate Raf-1 kinase inhibitor protein (RKIP), which promotes apoptosis. In combination with chemotherapy, immunotherapeutics overcome resistance in greater than 50% of NHL patients. Particles targeting CD20 may also be effective in drug resistant NHL.

[0005] Autoimmune disorders and cancers including NHL are currently being treated by surgery, radiotherapy, chemotherapy, and more recently immunotherapy. Substantial efforts have been expended to explore these modalities, but more innovative ideas are needed to gain ground against tumor resistance. In addition, many cancer therapeutics have an associated risk of cytotoxicity to healthy tissue. Therefore, there is a need in the art for therapeutics with reduced toxicity.

SUMMARY

[0006] Disclosed herein are recombinant polypeptides, methods and compositions for the specific targeting scFv-ELPs to cells. One aspect relates to a recombinant polypeptide comprising, or alternatively consisting essentially of, or yet further consisting of an elastin-like peptide (ELP) and a scFv, or a biological equivalent of the scFv. A scFv refers to a single-chain variable fragment of an antibody or ligand.

[0007] Another aspect relates to isolated polynucleotides encoding the recombinant scFv-ELP polypeptides as described herein. Further aspects relate to vectors and/or host cells comprising the polynucleotides encoding the recombinant scFv-ELP. In yet further aspects relate to compositions comprising, or alternatively consisting essentially of, or yet

further consisting of at least two polypeptides, described herein, organized in a cylindrical particle or a spherical particle, further consisting of a core comprised of the scFv of the recombinant polypeptide. In still further aspects, compositions comprising, or alternatively consisting essentially of, or yet further consisting of a carrier and the polypeptide described herein, a polynucleotide described herein, or vectors and/or host cells comprising, or alternatively consisting essentially of, or yet further consisting of a polynucleotide described herein.

[0008] Further aspects relate to methods for preparing a therapeutic polypeptide, comprising, or alternatively consisting essentially of, or yet further consisting of: expressing the polypeptide of this disclosure in a suitable expression system. Still further aspects relate to methods for denaturing and refolding the polypeptide of this disclosure. Also provided are methods of denaturing and refolding of the polypeptide at least twice, or at least thrice, or at least four times.

[0009] Another method aspect relates to a method for inducing apoptosis of a CD20+ cell comprising, or alternatively consisting essentially of, or yet further consisting of contacting the cell with an effective amount of the polypeptide of a recombinant scFv-ELP polypeptide described herein where the scFv component of the ELP is the single chain variable region from the anti-CD20 antibody. Also provided are methods for CD20-related disorder such as treating CD20 expressing cancer or autoimmune disease, comprising, or alternatively consisting essentially of, or yet further consisting of administering to a patient in need of such treatment a recombinant scFv-ELP polypeptide described herein where the scFv component of the ELP is the single chain variable region from the anti-CD20 antibody or administering the polynucleotide encoding such polypeptides.

[0010] A further aspect relates to a method for targeting a scFv-ELP to a cell comprising, or alternatively consisting essentially of, or yet further consisting of contacting the cell with an effective amount of the polypeptide described herein, wherein the scFv component of the scFv-ELP binds to a cellular component of the cell. The method is useful therapeutically and to screen for new molecules or agents that may affect the apoptotic pathway. For example, a test drug or agent is contacted with the cell, the polypeptide under conditions favorable to binding of the polypeptide to the cell receptor. The ability of the agent to inhibit the binding of the polypeptide to the cell receptor would be an indication that the test drug or agent is a candidate therapeutic for regulation of the cell through that receptor, e.g., apoptosis through binding of the CD20 cell surface receptor.

BRIEF DESCRIPTION OF THE FIGURES

[0011] FIGS. 1A-1C show phase diagrams of ELP and scFv ELP fusions. FIG. 1A: Phase diagram of ELP A192; FIG. 1B: Phase diagram of scFv A192; and FIG. 1C: Linear regression shows a concentration dependent change in transition temperature.

[0012] FIG. 2 shows the crosslinking of surface bound CD20 by a secondary antibody promotes translocation of the cross-linked complex to lipid rafts causing downstream signaling of apoptotic pathways.

[0013] FIG. 3 depicts the structure of the scFv-ELP. The scFv fragment was genetically fused to the N-terminus of ELP. The ELP was fused to the variable light chain of the scFv. The plasmid containing the fusion was transformed into *E. coli* and expressed.

[0014] FIGS. 4A-4B demonstrate the properties of the genetically expressed scFv ELP fusions. FIG. 4A: scFv A192 can be purified using inverse temperature cycling (ITC). R-Reducing conditions, NP-Non-reducing conditions FIG. 4B: scFv A192 assembles particles with hydrodynamic radius of ~ 32 nm whereas A192 is ~ 6 nm.

[0015] FIGS. 5A-5B depict the genetically expressed scFv assemble monodisperse spherical particles. FIG. 5A: Uranyl Acetate contrast enhanced transmission electron microscopy (TEM) images of scFv A192 reveals nanoparticles, which are 51.7 ± 12.4 nm wide. FIG. 5B: Cryo TEM images of scFv A192 show monodisperse particles of 48.1 ± 11.8 nm in diameter. Scale bar represents 50 nm.

[0016] FIG. 6 shows that scFv fusion reduces ELP transition temperature. Fusion of scFv to the ELP drops the transition temperature $\sim 20^\circ$ C. The drop in transition temperature correlates with nanoparticle assembly.

[0017] FIGS. 7A-H demonstrates scFv CD20 recognition using confocal microscopy. Panels A to D show Rhodamine (RHD) labeled scFv A192 forms distinct punctate bodies on Raji cell surface. Panels E to H show no scFv A192 binding on CEM cells.

[0018] FIGS. 8A-F show the recognition of CD20 surface antigen by the scFv-ELPs. FIGS. 8A to 8C show RHD labeled scFv A192 forms distinct punctate bodies on CD20⁺ Raji cell surface. FIGS. 8D-F show no scFv A192 binding on CD20⁻ CEM cells.

[0019] FIGS. 9A-9H show that unlabeled CD20 antibody abolishes scFv CD20 binding. Antibody treated CD20⁺ Raji cells, FIG. 9A-D, show no scFv A192 binding. Untreated Raji cells, FIG. 9E-H show scFv A192 binding.

[0020] FIG. 10 (right and left panels) show scFv ELP induce Raji cell apoptosis. Annexin V staining show induction of apoptosis in CD20⁺ Raji cells (Left) and not in CD20⁻ CEM cells (Right).

[0021] FIG. 11 depicts a MTS assay that shows selective killing of CD20⁺ Raji cells. The high IC₅₀ of scFv ELP can be attributed to self-assembly of scFv ELP into nanoparticles initiated by the scFv tag.

[0022] FIGS. 12A-F show that scFv ELP induce Raji cell apoptosis. Annexin V (ANX) staining show induction of apoptosis in CD20⁺ Raji cells (top) and not in CD20⁻ CEM cells (bottom).

[0023] FIG. 13 depicts the scheme used to make the scFv-ELP DNA constructs described in Example 1.

[0024] FIGS. 14A-14B show that Antibody Core Protein Polymer Nanoworms (ACPPNs) enhance apoptotic signaling. FIG. 14A: Expression of a fusion between a single chain antibody (scFv) and an environmentally-responsive protein polymer (i.e. ELPs) yields stable nanoworms. The nanoworms target cell-surface CD20 receptor, inducing apoptosis in B-cells and hence will be ideal for lymphoma therapies. FIG. 14B: An anti-CD20 scFv consisting of both a heavy and light chain was fused to the amino terminus of an elastin-like polypeptide (ELP). The ELP protein polymer, A192, was selected to promote solubility at physiological conditions and phase separation upon binding the cell surface.

[0025] FIGS. 15A-15B depict renaturation of scFv fusion forms ACPPNs. FIG. 15A: cryoTEM images of 'raw' scFv fusion form spherical assemblies with a diameter of 48.1 ± 11.8 nm. FIG. 15B: cryoTEM images of 'refolded' particles show a major population of 'nanoworms' with lengths of 56.2 ± 15.9 nm with a minor spherical particles with a diameter of 27.4 ± 7.5 nm. Scale bar represents 100 nm.

[0026] FIGS. 16A-16C show that ACPPNs competitively target CD20⁺ cells. FIG. 16A: Panels i-iii and vii-ix show CD20 recognition by RHD labeled RTXN on both Raji and SU-DHL-7 cells. RHD labeled RTXN forms a ring pattern around the target cell. Crosslinking surface bound RTXN by a 2^o goat Anti human Fc (Panels iv-vi and x-xii) shows the ring pattern shift to a more punctate appearance. FIG. 16B: Panels i-iii show recognition of surface CD20 by RHD labeled ACPPNs. ACPPNs binding also forms a punctate appearance similar to crosslinked RTXN. FIG. 16C: ACPPNs binding was significantly higher than unmodified A192 and RTXN block ($P=0.031^*$, 0.038^{**}). Normalized intensity of RHD was calculated using image J ($n=4$ slides). Scale bar represents 5 μ m.

[0027] FIGS. 17A-17F show ACPPNs reduce viability of CD20⁺ human lymphoma cell lines by inducing apoptosis. FIG. 17A: Trypan blue exclusion showed a significant increase in trypan blue positive cells with increasing concentrations of ACPPNs. FIG. 17B: CD20⁺ cells, Raji, and SU-DHL-7, show a concentration dependent reduction in cell viability. The calculated IC₅₀s for Raji and SU-DHL-7 are 32 and 41 μ M respectively. CD20⁻, CEM, are less effected by ACPPNs treatment. The IC₅₀ for CEM cells is 294 μ M which is ten times higher than ACPPNs. FIG. 17C: Raji and SU-DHL-7 cells both show an significant increase in ANXV/PI staining after ACPPNs treatment when compared to plain RTXN ($P=0.003^*$, $P=0.0005^{**}$). RTXN crosslinked by 2^o GAH and apoptosis control, chLym-1, both induce apoptosis. FIG. 17D: TUNEL staining confirms ACPPNs induction of apoptosis. ACPPNs outperform plain RTXN in both cell lines ($P=0.006^*$, $P=0.006^{**}$). ACPPNs induces apoptosis to the same extent as 2^o GAH crosslinked RTXN. FIGS. 17E-F: ACPPN treatment substantially increased caspase activity in both Raji and SU-DHL-7 cells.

[0028] FIGS. 18A-18J show that ACPPNs treatment shows relatively high tumor accumulation and reduces tumor burden in Raji xenografts. FIGS. A-H: ACPPNs microdistribution (2.5 mgs/dose, $n=3$) using laser confocal microscopy shows accumulation of RHD labeled ACPPNs in liver (A, E), spleen (B, F), tumor (C, G), and kidney (D, H). There was minimal accumulation of these particles in the lungs and heart. Interestingly particle accumulation can be seen in the spleen marginal zone (MZ) and the bowman capsule (BC). Scale bar represents 20 μ m. FIG. 18I: As of day 25, ACPPNs significantly reduced mean tumor burden when compared to PBS and RTXN treated groups ($n=5$ /group, $P=0.0011$). FIG. 18J: ACPPNs treatment significantly enhances survival when compared to PBS and RTXN control groups ($P=0.013$). The highlighted tick marks indicate days of dose administration.

DETAILED DESCRIPTION

Definitions

[0029] The practice of the present invention will employ, unless otherwise indicated, conventional techniques of tissue culture, immunology, molecular biology, microbiology, cell biology and recombinant DNA, which are within the skill of the art. See, e.g., Sambrook et al., (1989) *Molecular Cloning: A Laboratory Manual*, 2nd edition; Ausubel et al., eds. (1987) *Current Protocols In Molecular Biology*; MacPherson, B. D. Hames and G. R. Taylor eds., (1995) *PCR 2: A Practical Approach*; Harlow and Lane, eds. (1988) *Antibodies, A Labo-*

ratory Manual; Harlow and Lane, eds. (1999) Using Antibodies, a Laboratory Manual; and R. I. Freshney, ed. (1987) Animal Cell Culture.

[0030] All numerical designations, e.g., pH, temperature, time, concentration, and molecular weight, including ranges, are approximations which are varied (+) or (−) by increments of 1.0 or 0.1, as appropriate. It is to be understood, although not always explicitly stated that all numerical designations are preceded by the term “about”. It also is to be understood, although not always explicitly stated, that the reagents described herein are merely exemplary and that equivalents of such are known in the art.

[0031] As used in the specification and claims, the singular form “a,” “an” and “the” include plural references unless the context clearly dictates otherwise.

[0032] As used herein, the term “comprising” is intended to mean that the compositions and methods include the recited elements, but do not exclude others. “Consisting essentially of” when used to define compositions and methods, shall mean excluding other elements of any essential significance to the combination when used for the intended purpose. Thus, a composition consisting essentially of the elements as defined herein would not exclude trace contaminants or inert carriers. “Consisting of” shall mean excluding more than trace elements of other ingredients and substantial method steps. Embodiments defined by each of these transition terms are within the scope of this invention.

[0033] A “composition” is also intended to encompass a combination of active agent and another carrier, e.g., compound or composition, inert (for example, a detectable agent or label) or active, such as an adjuvant, diluent, binder, stabilizer, buffers, salts, lipophilic solvents, preservative, adjuvant or the like. Carriers also include pharmaceutical excipients and additives proteins, peptides, amino acids, lipids, and carbohydrates (e.g., sugars, including monosaccharides, di-, tri-, tetra-, and oligosaccharides; derivatized sugars such as alditols, aldonic acids, esterified sugars and the like; and polysaccharides or sugar polymers), which can be present singly or in combination, comprising alone or in combination 1-99.99% by weight or volume. Exemplary protein excipients include serum albumin such as human serum albumin (HSA), recombinant human albumin (rHA), gelatin, casein, and the like. Representative amino acid/antibody components, which can also function in a buffering capacity, include alanine, glycine, arginine, betaine, histidine, glutamic acid, aspartic acid, cysteine, lysine, leucine, isoleucine, valine, methionine, phenylalanine, aspartame, and the like. Carbohydrate excipients are also intended within the scope of this invention, examples of which include but are not limited to monosaccharides such as fructose, maltose, galactose, glucose, D-mannose, sorbose, and the like; disaccharides, such as lactose, sucrose, trehalose, cellobiose, and the like; polysaccharides, such as raffinose, melezitose, maltodextrins, dextrans, starches, and the like; and alditols, such as mannitol, xylitol, maltitol, lactitol, xylitol sorbitol (glucitol) and myoinositol.

[0034] The term “pharmaceutically acceptable carrier” (or medium), which may be used interchangeably with the term biologically compatible carrier or medium, refers to reagents, cells, compounds, materials, compositions, and/or dosage forms that are not only compatible with the cells and other agents to be administered therapeutically, but also are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other com-

plication commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable carriers suitable for use in the present invention include liquids, semi-solid (e.g., gels) and solid materials (e.g., cell scaffolds and matrices, tubes sheets and other such materials as known in the art and described in greater detail herein). These semi-solid and solid materials may be designed to resist degradation within the body (non-biodegradable) or they may be designed to degrade within the body (biodegradable, bioerodable). A biodegradable material may further be bioresorbable or bioabsorbable, i.e., it may be dissolved and absorbed into bodily fluids (water-soluble implants are one example), or degraded and ultimately eliminated from the body, either by conversion into other materials or breakdown and elimination through natural pathways.

[0035] A “pharmaceutical composition” is intended to include the combination of an active agent with a carrier, inert or active, making the composition suitable for diagnostic or therapeutic use in vitro, in vivo or ex vivo.

[0036] As used herein, the term “patient” or “subject” intends an animal, a mammal or yet further a human patient. For the purpose of illustration only, a mammal includes but is not limited to a human, a feline, a canine, a simian, a murine, a bovine, an equine, a porcine or an ovine.

[0037] The term “purified protein or peptide” as used herein, is intended to refer to a composition, isolatable from other components, wherein the protein or peptide is purified to any degree relative to its naturally-obtainable state. A purified protein or peptide therefore also refers to a protein or peptide, free from the environment in which it may naturally occur.

[0038] The term “therapeutic” refers to an agent or component capable of inducing a biological effect in vivo and/or in vitro. The biological effect may be useful for treating and/or preventing a condition, disorder, or disease in a subject or patient. A therapeutic may include, without limitation, a small molecule, a nucleic acid, or a polypeptide.

[0039] As used herein, the term “CD20” or “B-lymphocyte antigen CD20” refers to a protein expressed on the surface of B-cells. In humans, CD20 is encoded by the MS4A1 gene. “Anti-CD20” or “Anti-CD20 antibody” refers to an antibody that specifically recognizes the CD20 antigen. Some current therapeutics are anti-CD20 antibodies. These include, for example, Rituximab, Ofatumumab, AME-133v (by Applied Molecular Evolution), Ocrelizumab for multiple sclerosis, TRU-015 (by Trubion), and IMMU-106 (veltuzumab).

[0040] As used herein, the term “biological equivalent thereof” is used synonymously with “equivalent” unless otherwise specifically intended. When referring to a reference protein, polypeptide or nucleic acid, the term intends those having minimal homology while still maintaining desired structure or functionality. Unless specifically recited herein, it is contemplated that any polynucleotide, polypeptide or protein mentioned herein also includes equivalents thereof. For example, an equivalent intends at least about 60%, or 65%, or 70%, or 75%, or 80% homology or identity and alternatively, at least about 85%, or alternatively at least about 90%, or alternatively at least about 95%, or alternatively 98% percent homology or identity and exhibits substantially equivalent biological activity to the reference protein, polypeptide or nucleic acid. Alternatively, a biological equivalent is a peptide encoded by a nucleic acid that hybridizes under stringent conditions to a nucleic acid or complement that encodes the peptide. Hybridization reactions can be performed under conditions of different “stringency”. In general, a low stringency

hybridization reaction is carried out at about 40° C. in about 10×SSC or a solution of equivalent ionic strength/temperature. A moderate stringency hybridization is typically performed at about 50° C. in about 6×SSC, and a high stringency hybridization reaction is generally performed at about 60° C. in about 1×SSC. Hybridization reactions can also be performed under “physiological conditions” which is well known to one of skill in the art. A non-limiting example of a physiological condition is the temperature, ionic strength, pH and concentration of Mg²⁺ normally found in a cell. An equivalent polynucleotide is one that hybridizes under stringent conditions to the reference polynucleotide or the complement of the reference polynucleotide, in one aspect, having similar biological activity as the reference polynucleotide.

[0041] A polynucleotide or polynucleotide region (or a polypeptide or polypeptide region) having a certain percentage (for example, about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 97%) of “sequence identity” to another sequence means that, when aligned, that percentage of bases (or amino acids) are the same in comparing the two sequences. The alignment and the percent homology or sequence identity can be determined using software programs known in the art, for example those described in *Current Protocols in Molecular Biology* (Ausubel et al., eds. 1987) Supplement 30, section 7.7.18, Table 7.7.1. Preferably, default parameters are used for alignment. A preferred alignment program is BLAST, using default parameters. In particular, preferred programs are BLASTN and BLASTP, using the following default parameters: Genetic code=standard; filter=none; strand=both; cutoff=60; expect=10; Matrix=BLOSUM62; Descriptions=50 sequences; sort by=HIGH SCORE; Databases=non-redundant, GenBank+EMBL+DDBJ+PDB+GenBank CDS translations+SwissProt+SPupdate+PIR. Details of these programs can be found at the following Internet address: ncbi.nlm.nih.gov/cgi-bin/BLAST.

[0042] “Homology” or “identity” or “similarity” refers to sequence similarity between two peptides or between two nucleic acid molecules. Homology can be determined by comparing a position in each sequence which may be aligned for purposes of comparison. When a position in the compared sequence is occupied by the same base or amino acid, then the molecules are homologous at that position. A degree of homology between sequences is a function of the number of matching or homologous positions shared by the sequences. An “unrelated” or “non-homologous” sequence shares less than 40% identity, or alternatively less than 25% identity, with one of the sequences of the present invention.

[0043] An “equivalent” of a polynucleotide or polypeptide refers to a polynucleotide or a polypeptide having a substantial homology or identity to the reference polynucleotide or polypeptide or one that hybridizes under conditions of high stringency to the reference polynucleotide or its complement. An equivalent polypeptide is encoded by a polynucleotide that hybridizes to a polynucleotide or its complement that expresses the reference polypeptide. In one aspect, a “substantial homology” is greater than about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 98% homology.

[0044] As used herein, “expression” refers to the process by which polynucleotides are transcribed into mRNA and/or the process by which the transcribed mRNA is subsequently being translated into peptides, polypeptides, or proteins. If the

polynucleotide is derived from genomic DNA, expression may include splicing of the mRNA in an eukaryotic cell.

[0045] The term “encode” as it is applied to polynucleotides refers to a polynucleotide which is said to “encode” a polypeptide if, in its native state or when manipulated by methods well known to those skilled in the art, it can be transcribed and/or translated to produce the mRNA for the polypeptide and/or a fragment thereof. The antisense strand is the complement of such a nucleic acid, and the encoding sequence can be deduced therefrom.

[0046] “Regulatory polynucleotide sequences” intends any one or more of promoters, operons, enhancers, as known to those skilled in the art to facilitate and enhance expression of polynucleotides.

[0047] An “expression vehicle” is a vehicle or a vector, non-limiting examples of which include viral vectors or plasmids, that assist with or facilitate expression of a gene or polynucleotide that has been inserted into the vehicle or vector.

[0048] A “delivery vehicle” is a vehicle or a vector that assists with the delivery of an exogenous polynucleotide into a target cell. The delivery vehicle may assist with expression or it may not, such as traditional calcium phosphate transfection compositions.

[0049] The term “scFv” refers to a single-chain variable fragment. scFv is a fusion protein of the variable regions of the heavy (VH) and light chains (VL) of immunoglobulins, connected with a linker peptide. The linker peptide can be from about 5 to 40 amino acids or from about 10 to 30 amino acids or about 5, 10, 15, 20, 25, 30, 35, or 40 amino acids in length. Single-chain variable fragments lack the constant Fc region found in complete antibody molecules, and, thus, the common binding sites (e.g., Protein G) used to purify antibodies. These fragments can often be purified or immobilized using Protein L, since Protein L interacts with the variable region of kappa light chains. More commonly, scientists incorporate a six histidine tag (SEQ ID NO: 15) on the c-terminus of the scFv molecule and purify them using immobilized metal affinity chromatography (IMAC). For unknown reasons, some scFv can also be captured by Protein A.

[0050] “An effective amount” refers to the amount of an active agent or a pharmaceutical composition sufficient to induce a desired biological and/or therapeutic result. That result can be alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. The effective amount will vary depending upon the health condition or disease stage of the subject being treated, timing of administration, the manner of administration and the like, all of which can be determined readily by one of ordinary skill in the art.

[0051] As used herein, the terms “treating,” “treatment” and the like are used herein to mean obtaining a desired pharmacologic and/or physiologic effect. The effect may be prophylactic in terms of completely or partially preventing a disorder or sign or symptom thereof, and/or may be therapeutic in terms of a partial or complete cure for a disorder and/or adverse effect attributable to the disorder.

[0052] As used herein, the term CD20+ or CD20-related disorder intends a disease or condition marked by the expression of the CD20 receptor on the diseased or cell or tissue. In one aspect the disease is cancer such as lymphoma (non-Hodgkin’s lymphoma) or CD20 expressing leukemias. In another aspect, the disease is an autoimmune disease such as Sjogren’s syndrome, rheumatoid arthritis, coeliac disease,

Crohn's disease and systemic lupus erythematosus. Tarella et al. (2013) *Autoimmunity Reviews* 12:802-813. In another aspect, a CD20-related disorder is any that has been treated by conventional CD20 antibody therapies such as rituximab.

[0053] As used herein, the term "nanoparticle" and "nanoworm" are intended to encompass the ELP-antibody fusion constructs unless otherwise noted. Applicants have discovered that denaturing and renaturing the nanoparticles will yield nanoworms having distinct dimensions from the more spherical nanoparticles.

[0054] As used herein, to "treat" further includes systemic amelioration of the symptoms associated with the pathology and/or a delay in onset of symptoms. Clinical and sub-clinical evidence of "treatment" will vary with the pathology, the subject and the treatment.

[0055] As used herein, an "antibody" includes whole antibodies and any antigen binding fragment or a single chain thereof. Thus the term "antibody" includes any protein or peptide containing molecule that comprises at least a portion of an immunoglobulin molecule. Examples of such include, but are not limited to a complementarity determining region (CDR) of a heavy or light chain or a ligand binding portion thereof, a heavy chain or light chain variable region, a heavy chain or light chain constant region, a framework (FR) region, or any portion thereof, or at least one portion of a binding protein, any of which can be incorporated into an antibody of the present invention. The term "antibody" is further intended to encompass digestion fragments, specified portions, derivatives and variants thereof, including antibody mimetics or comprising portions of antibodies that mimic the structure and/or function of an antibody or specified fragment or portion thereof, including single chain antibodies and fragments thereof. It also includes in some aspects, antibody variants, polyclonal antibodies, human antibodies, humanized antibodies, chimeric antibodies, antibody derivatives, a bispecific molecule, a multispecific molecule, a heterospecific molecule, heteroantibodies and human monoclonal antibodies.

[0056] Examples of binding fragments encompassed within the term "antigen binding portion" of an antibody include a Fab fragment, a monovalent fragment consisting of the V_L , V_H , C_L and CH, domains; a F(ab')₂ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragment consisting of the V_H and C_H , domains; a Fv fragment consisting of the V_L and V_H domains of a single arm of an antibody, a dAb fragment (Ward et al. (1989) *Nature* 341:544-546), which consists of a V_H domain; and an isolated complementarity determining region (CDR). Furthermore, although the two domains of the Fv fragment, V_L and V_H , are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the V_L and V_H regions pair to form monovalent molecules (known as single chain Fv (scFv)). Bird et al. (1988) *Science* 242:423-426 and Huston et al. (1988) *Proc. Natl. Acad. Sci. USA* 85:5879-5883. Single chain antibodies are also intended to be encompassed within the term "fragment of an antibody." Any of the above-noted antibody fragments are obtained using conventional techniques known to those of skill in the art, and the fragments are screened for binding specificity and neutralization activity in the same manner as are intact antibodies.

[0057] "Administration" can be effected in one dose, continuously or intermittently throughout the course of treatment. Methods of determining the most effective means and

dosage of administration are known to those of skill in the art and will vary with the composition used for therapy, the purpose of the therapy, the target cell being treated, and the subject being treated. Single or multiple administrations can be carried out with the dose level and pattern being selected by the treating physician. Suitable dosage formulations and methods of administering the agents are known in the art. Route of administration can also be determined and method of determining the most effective route of administration are known to those of skill in the art and will vary with the composition used for treatment, the purpose of the treatment, the health condition or disease stage of the subject being treated, and target cell or tissue. Non-limiting examples of route of administration include oral administration, nasal administration, injection, topical application, intrapentoneal, intravenous and by inhalation. An agent of the present invention can be administered for therapy by any suitable route of administration. It will also be appreciated that the preferred route will vary with the condition and age of the recipient, and the disease being treated.

[0058] The agents and compositions of the present invention can be used in the manufacture of medicaments and for the treatment of humans and other animals by administration in accordance with conventional procedures, such as an active ingredient in pharmaceutical compositions.

[0059] As used herein, the term "detectable label" intends a directly or indirectly detectable compound or composition that is conjugated directly or indirectly to the composition to be detected. In one aspect, the detectable label is a non-naturally occurring detectable label in that it is not normally associated with the compound or composition as found in nature. In another aspect, a combination of a compound or composition and detectable label excludes combination that occur in nature. Non-limiting examples of such tags include, e.g., N-terminal histidine tags (N-His), magnetically active isotopes, e.g., ¹¹⁵Sn, ¹¹⁷Sn and ¹¹⁹Sn, a non-radioactive isotopes such as ¹³C and ¹⁵N, polynucleotide or protein such as an antibody so as to generate a "labeled" composition. For example, a radioisotope is not attached to a nucleic acid in nature. The term also includes sequences conjugated to the polynucleotide that will provide a signal upon expression of the inserted sequences, such as green fluorescent protein (GFP) and the like. The label may be detectable by itself (e.g. radioisotope labels or fluorescent labels) or, in the case of an enzymatic label, may catalyze chemical alteration of a substrate compound or composition which is detectable. The labels can be suitable for small scale detection or more suitable for high-throughput screening. As such, suitable labels include, but are not limited to magnetically active isotopes, non-radioactive isotopes, radioisotopes, fluorochromes, luminescent compounds, dyes, and proteins, including enzymes. The label may be simply detected or it may be quantified. A response that is simply detected generally comprises a response whose existence merely is confirmed, whereas a response that is quantified generally comprises a response having a quantifiable (e.g., numerically reportable) value such as an intensity, polarization, and/or other property. In luminescence or fluorescence assays, the detectable response may be generated directly using a luminophore or fluorophore associated with an assay component actually involved in binding, or indirectly using a luminophore or fluorophore associated with another (e.g., reporter or indicator) component.

[0060] Examples of luminescent labels that produce signals include, but are not limited to bioluminescence and chemiluminescence. Detectable luminescence response generally comprises a change in, or an occurrence of, a luminescence signal. Suitable methods and luminophores for luminescently labeling assay components are known in the art and described for example in Haugland, Richard P. (1996) *Handbook of Fluorescent Probes and Research Chemicals* (6th ed.). Examples of luminescent probes include, but are not limited to, aequorin and luciferases.

[0061] Examples of suitable fluorescent labels include, but are not limited to, fluorescein, rhodamine, tetramethylrhodamine, eosin, erythrosin, coumarin, methyl-coumarins, pyrene, Malacite green, stilbene, Lucifer Yellow, Cascade Blue™, and Texas Red. Other suitable optical dyes are described in the Haugland, Richard P. (1996) *Handbook of Fluorescent Probes and Research Chemicals* (6th ed.).

[0062] In another aspect, the fluorescent label is functionalized to facilitate covalent attachment to a cellular component present in or on the surface of the cell or tissue such as a cell surface marker. Suitable functional groups, including, but not are limited to, isothiocyanate groups, amino groups, haloacetyl groups, maleimides, succinimidyl esters, and sulfonyl halides, all of which may be used to attach the fluorescent label to a second molecule. The choice of the functional group of the fluorescent label will depend on the site of attachment to either a linker, the agent, the marker, or the second labeling agent.

Modes for Carrying Out the Disclosure

[0063] This disclosure relates to genetically engineered polypeptide nanoparticles targeted to CD20+ cells. To develop new treatments for CD20+ cancers (such as non-Hodgkin lymphoma, for example), new drug carriers are required that are biocompatible and easily modified with bioactive peptides. An emerging solution to this challenge utilizes genetically engineered polypeptides to drive the assembly of nanostructures. Elastin-like-polypeptide engages in a unique phase transition behavior, which can mediate self-assembly of nanoparticles. Described herein is a class of ELP fusion proteins with scFv fragments which are intended for inducing apoptosis in the target cell. The scFv-ELP fusion proteins are able to self-assemble to nanoparticles, which can also be utilized for gene therapy and drug delivery to the target cancerous cells.

Elastin-Like Polypeptides (ELPs)

[0064] Elastin-like-polypeptides (ELPs) are a genetically engineered polypeptide with unique phase behavior (see for e.g. S. R. MacEwan, et al., *Biopolymers* 94(1) (2010) 60-77) which promotes recombinant expression, protein purification and self-assembly of nanostructures (see for e.g. A. Chilkoti, et al., *Advanced Drug Delivery Reviews* 54 (2002) 1093-1111). ELPs are artificial polypeptides composed of repeated pentapeptide sequences, (Val-Pro-Gly-Xaa-Gly)_n (SEQ ID NO: 6) derived from human tropoelastin, where Xaa is the "guest residue" which is any amino acid. In one embodiment, Xaa is any amino acid except proline and n is an integer of at least one. This peptide motif displays rapid and reversible de-mixing from aqueous solutions above a transition temperature, *T_p*. Below *T_p*, ELPs adopt a highly water soluble random coil conformation; however, above *T_p*, they separate from solution, coalescing into a second aqueous phase. The *T_p*

of ELPs can be tuned by choosing the guest residue and ELP chain length as well as fusion peptides at the design level (see for e.g. MacEwan S R, et al., *Biopolymers* 94(1): 60-77). The ELP phase is both biocompatible and highly specific for ELPs or ELP fusion proteins, even in complex biological mixtures. Genetically engineered ELPs are monodisperse, biodegradable, non-toxic. Throughout this description, ELPs are identified by the single letter amino acid code of the guest residue followed by the number of repeat units, n. For example, S48I48 represents a diblock copolymer ELP with 48 serine (S) pentamers at the amino terminus and 48 isoleucine (I) pentamers at the carboxy terminus.

[0065] Described herein are ELP fusion proteins, which can be self-assembled into nanoparticles or nanoworms. The diameter of the substantially spherical nanoparticle can be from about 1 to about 1000 nm or from about 1 to about 500 nm, or from about 1 to about 100 nm, or from about 1 to about 50 nm, or from about 1 to 5 nm, or from about 3 to 20 nm, or from about 20 to about 50 nm, or from about 30 to about 50 nm, or from about 35 to about 45 nm. In one embodiment, the diameter is about 30 nm. The length of the nanoworm can be from about 10 to 1000 nm, or from about 10 to 500 nm, or from about 1 to about 100 nm or from about 5 to about 75 nm, or from about 5 to about 75 nm, or from about 10 to about 50 nm, or from about 15 to about 65 nm, or from about 10 to about 65 nm, or from about 15 to about 60 nm. The width of the nanoworm can be from about 50 to 1 nm, or from about 40 to 1 nm, or from about 35 to about 1 nm or from about 30 to about 1 nm, or from about 25 to about 1 nm, or from about 20 to about 1 nm. The fusion proteins are composed of elastin-like-polypeptides and high affinity polypeptides. These fusion proteins can be expressed from a variety of expression systems known to those skilled in the art and easily purified by the phase transition behavior of ELPs. These ELP fusion proteins are able to conjugate small molecules, such as, for example, chemotherapeutic agents, anti-inflammation agents, antibiotics and polypeptides such as antibodies and antibody fragments and other water soluble drugs. In addition, the ELP nanoparticles are useful for carrying DNA, RNA, protein and peptide-based therapeutics.

[0066] ELPs have potential advantages over chemically synthesized polymers as drug delivery agents. First, because they are biosynthesized from a genetically encoded template, ELPs can be made with precise molecular weight. Chemical synthesis of long linear polymers does not typically produce an exact length, but instead a range of lengths. Consequently, fractions containing both small and large polymers yield mixed pharmacokinetics and biodistribution. Second, ELP biosynthesis produces very complex amino acid sequences with nearly perfect reproducibility. This enables very precise selection of the location of drug attachment. Thus drug can be selectively placed on the corona, buried in the core, or dispersed equally throughout the polymer. Third, ELP can self-assemble into multivalent nanoparticles that can have excellent site-specific accumulation and drug carrying properties. Fourth, because ELP are designed from native amino acid sequences found extensively in the human body they are biodegradable, biocompatible, and tolerated by the immune system. Fifth, ELPs undergo an inverse phase transition temperature, *T_p*, above which they phase separate into large aggregates. By localized heating, additional ELP can be drawn into the target site, which may be beneficial for increasing drug concentrations.

[0067] A therapeutic such as a drug, for example, may be attached to the ELP through cysteine, lysine, glutamic acid or aspartic acid residues present in the polymer. In some embodiments, the cysteine, lysine, glutamic acid or aspartic acid residues are generally present throughout the length of the polymer. In some embodiments, the cysteine, lysine, glutamic acid or aspartic acid residues are clustered at the end of the polymer. In some embodiments of the presently described subject matter, therapeutics are attached to the cysteine residues of the ELP using thiol reactive linkers. In some embodiments of the presently described subject matter, therapeutics are attached to the lysine residues of the high molecular weight polymer sequence using NHS (N-hydroxysuccinimide) chemistry to modify the primary amine group present on these residues. In some embodiments of the presently described subject matter, therapeutics are attached to the glutamic acid or aspartic acid residues of the ELP using EDC (1-Ethyl-3-[3-dimethylaminopropyl]carbodiimide Hydrochloride) chemistry to modify the carboxylic acid group present on the ELP residues.

[0068] The therapeutic associated with the ELP may be hydrophobic or hydrophilic. Which the drug is hydrophobic, attachment to the terminus of the ELP may facilitate formation of the multivalent nanoparticle. The number of drug particles attached to the ELP can be from about 1 to about 30, or from about 1 to about 10, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In some embodiments, the attachment points for a therapeutic are equally distributed along the backbone of the ELP, and the resulting drug-ELP is prevented from forming nanoparticle structures under physiological salt and temperature conditions.

[0069] In addition to therapeutics, the ELPs may also be associated with a detectable label that allows for the visual detection of in vivo uptake of the ELPs. Suitable labels include, for example, fluorescein, rhodamine, tetramethylrhodamine, eosin, erythrosin, coumarin, methyl-coumarins, pyrene, Malachite green, Alexa-Fluor®, stilbene, Lucifer Yellow, Cascade Blue™, and Texas Red. Other suitable optical dyes are described in Hargland, Richard P. (1996) *Molecular Probes Handbook*.

[0070] In certain embodiments, the ELP components comprise, or alternatively consist essentially of, or yet further consist of: polymeric or oligomeric repeats of the pentapeptide [VPGXG]_n (SEQ ID NO: 6), where the guest residue X is any amino acid, that in one aspect, excludes proline and n is the number of repeats. X may be a naturally occurring or non-naturally occurring amino acid. In some embodiments, X is selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, serine, threonine, tryptophan, tyrosine and valine. In some embodiments, X is a natural amino acid other than proline or cysteine. In a further embodiment, the ELP comprises, or alternatively consists essentially of, or yet further consists of: the primary sequence of [VPGAG]_n (SEQ ID NO: 7), [VPGAG]_n[VPGIG]_n (SEQ ID NO: 8), or [VPGSG]_n[VPGIG]_n (SEQ ID NO: 9). "n" or the number of repeats can be from the group of about 1 to 500, about 30-500, about 20-200, about 20-100, about 30-200, about 40-200, about 45-200, about 30-100, about 40-100, about 45-100, about 20, about 35, about 40, about 45, about 50, about 55, about 60, about 65, about 70, about 75, about 80, about 85, about 90, about 100, about 105, about 110, about 120, about 130, about 140, about 150, about

160, about 170, about 180, about 190, or about 200. In certain embodiments, n is about 96, about 48, or about 192.

[0071] The guest residue X may be a non-classical (non-genetically encoded) amino acid. Examples of non-classical amino acids include: D-isomers of the common amino acids, 2,4-diaminobutyric acid, α-amino isobutyric acid, A-aminobutyric acid, Abu, 2-amino butyric acid, γ-Abu, ε-Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, β-alanine, fluoro-amino acids, designer amino acids such as β-methyl amino acids, C α-methyl amino acids, N α-methyl amino acids, and amino acid analogs in general.

[0072] Selection of X is independent in each ELP structural unit (e.g., for each structural unit defined herein having a guest residue X). For example, X may be independently selected for each structural unit as an amino acid having a positively charged side chain, an amino acid having a negatively charged side chain, or an amino acid having a neutral side chain, including in some embodiments, a hydrophobic side chain.

[0073] In each embodiment, the structural units, or in some cases polymeric or oligomeric repeats, of the ELP sequences may be separated by one or more amino acid residues that do not eliminate the overall effect of the molecule, that is, in imparting certain improvements to the therapeutic component as described. In certain embodiments, such one or more amino acids also do not eliminate or substantially affect the phase transition properties of the ELP component (relative to the deletion of such one or more amino acids).

[0074] The ELP component in some embodiments is selected or designed to provide a T_i ranging from about 10 to about 80° C., such as from about 35 to about 60° C., or from about 38 to about 45° C. In some embodiments, the T_i is greater than about 40° C. or greater than about 42° C., or greater than about 45° C., or greater than about 50° C. The transition temperature, in some embodiments, is above the body temperature of the subject or patient (e.g., >37° C.) thereby remaining soluble in vivo, or in other embodiments, the T_i is below the body temperature (e.g., <37° C.) to provide alternative advantages, such as in vivo formation of a drug depot for sustained release of the therapeutic agent. For example, the transition temperature may be about 38, about 39, about 40, about 41, about 42, about 43, about 44, about 45, about 50, about 55, about 60, about 65, or about 70° C. In further embodiments, the transition temperature is at or below physiological level such that the ELPs are assembled into nanoparticles when administered to a patient. In some embodiments, the transition temperature of the ELP-scFv is less than or equal to 37° C. In further embodiments, the transition temperature is about 36, about 35, about 34, about 33, about 32, about 31, about 30, about 29, about 28, about 27, about 26, about 25, about 20, about 15, or about 10° C.

[0075] The T_i of the ELP component can be modified by varying ELP chain length. For polypeptides having a molecular weight >100,000, the hydrophobicity scale developed by Urry et al. (PCT/US96/05186, which is hereby incorporated by reference in its entirety) is preferred for predicting the approximate T_i of a specific ELP sequence. However, in some embodiments, ELP component length can be kept relatively small, while maintaining a target T_n by incorporating a larger fraction of hydrophobic guest residues (e.g., amino acid residues having hydrophobic side chains) in the ELP sequence.

For polypeptides having a molecular weight <100,000, the T_f may be predicted or determined by the following quadratic function: $T_f = M_0 + M_1X + M_2X^2$ where X is the MW of the fusion protein, and $M_0 = 116.21$; $M_1 = -1.7499$; $M_2 = 0.010349$.

[0076] While the T_f of the ELP component, and therefore of the ELP component coupled to a therapeutic component, is affected by the identity and hydrophobicity of the guest residue, X , additional properties of the molecule may also be affected. Such properties include, but are not limited to solubility, bioavailability, persistence, and half-life of the molecule.

scFv Polypeptides

[0077] Described herein are polypeptides comprising, or alternatively consisting essentially of, or yet further consisting of: an elastin-like peptide (ELP) and a scFv, or a biological equivalent of the scFv. These polypeptides may be referred to herein as “ELP fusions” “scFv fusions” “scFv assemblies” “antibody core protein polymer nanoworms” or “ACPPNs” and which are essentially synonymous. The scFv is a polypeptide that recognizes, has affinity, and/or binds to a specific antigen. In one embodiment, the scFv comprises, or alternatively consists essentially of or yet further consists of the single chain variable region from the anti-CD20 antibody. Examples of the single chain variable region from the scFv include the polypeptides of SEQ ID NOS: 1 and 2. In certain embodiments, the scFv comprises, or alternatively consists essentially of or yet further consists of the sequence of SEQ ID NO: 1 or SEQ ID NO: 2 or a biological equivalent thereof. In further embodiments, the scFv-ELP polypeptide corresponds to a sequence selected from the group consisting of SEQ ID NOS: 3, 4, and 5 or a biological equivalent thereof.

[0078] The scFv can have a peptide linker between the heavy and light chains. The linker is variable in length and, in certain embodiments, comprise amino acid residues such as glycine or serine. It is also within the scope of this disclosure to have scFvs with linker peptides that are too short for the two variable regions to fold together (about five amino acids), forcing scFvs to dimerize. This type is known as diabodies. Diabodies have been shown to have dissociation constants up to 40-fold lower than corresponding scFvs, meaning that they have a much higher affinity to their target. Consequently, diabody drugs could be dosed much lower than other therapeutic antibodies and are capable of highly specific targeting of tumors in vivo. Still shorter linkers (one or two amino acids) lead to the formation of trimers, so-called triabodies or tribodies. Tetrabodies have also been produced. They exhibit an even higher affinity to their targets than diabodies. All of these formats can be composed from variable fragments with specificity for two different antigens, in which case they are types of bispecific antibodies.

Expression of Recombinant Proteins

[0079] ELPs, ELP fusions and other recombinant proteins described herein can be prepared by expressing polynucleotides encoding the polypeptide sequences of this invention in an appropriate host cell, i.e., a prokaryotic or eukaryotic host cell. This can be accomplished by methods of recombinant DNA technology known to those skilled in the art. It is known to those skilled in the art that modifications can be made to any peptide to provide it with altered properties. Polypeptides of the invention can be modified to include unnatural amino acids. Thus, the peptides may comprise D-amino acids, a combination of D- and L-amino acids, and various “designer” amino acids (e.g., β -methyl amino acids,

C- α -methyl amino acids, and N- α -methyl amino acids, etc.) to convey special properties to peptides. Additionally, by assigning specific amino acids at specific coupling steps, peptides with α -helices, β turns, β sheets, α -turns, and cyclic peptides can be generated. Generally, it is believed that beta-turn spiral secondary structure or random secondary structure is preferred.

[0080] The ELPs can be expressed and purified from a suitable host cell system. Suitable host cells include prokaryotic and eukaryotic cells, which include, but are not limited to bacterial cells, yeast cells, insect cells, animal cells, mammalian cells, murine cells, rat cells, sheep cells, simian cells and human cells. Examples of bacterial cells include *Escherichia coli*, *Salmonella enterica* and *Streptococcus gordonii*. In one embodiment, the host cell is *E. coli*. The cells can be purchased from a commercial vendor such as the American Type Culture Collection (ATCC, Rockville Md., USA) or cultured from an isolate using methods known in the art. Examples of suitable eukaryotic cells include, but are not limited to 293T HEK cells, as well as the hamster cell line BHK-21; the murine cell lines designated NIH3T3, NSO, C127, the simian cell lines COS, Vero; and the human cell lines HeLa, PER.C6 (commercially available from Crucell) U-937 and Hep G2. A non-limiting example of insect cells include *Spodoptera frugiperda*. Examples of yeast useful for expression include, but are not limited to *Saccharomyces*, *Schizosaccharomyces*, *Hansenula*, *Candida*, *Torulopsis*, *Yarrowia*, or *Pichia*. See e.g., U.S. Pat. Nos. 4,812,405; 4,818,700; 4,929,555; 5,736,383; 5,955,349; 5,888,768 and 6,258,559.

Protein Purification

[0081] The phase transition behavior of the ELPs allows for easy purification. The ELPs may also be purified from host cells using methods known to those skilled in the art. These techniques involve, at one level, the crude fractionation of the cellular milieu to polypeptide and non-polypeptide fractions. Having separated the polypeptide from other proteins, the polypeptide of interest may be further purified using chromatographic and electrophoretic techniques to achieve partial or complete purification (or purification to homogeneity). Analytical methods particularly suited to the preparation of a pure peptide or polypeptide are filtration, ion-exchange chromatography, exclusion chromatography, polyacrylamide gel electrophoresis, affinity chromatography, or isoelectric focusing. A particularly efficient method of purifying peptides is fast protein liquid chromatography or even HPLC. In the case of ELP compositions, protein purification may also be aided by the thermal transition properties of the ELP domain as described in U.S. Pat. No. 6,852,834.

[0082] Additional techniques include, for example, precipitation with ammonium sulfate, PEG, antibodies and the like or by heat denaturation, followed by centrifugation; chromatography steps such as ion exchange, gel filtration, reverse phase, hydroxylapatite and affinity chromatography; isoelectric focusing; gel electrophoresis; and combinations of such and other techniques. As is generally known in the art, it is believed that the order of conducting the various purification steps may be changed, or that certain steps may be omitted, and still result in a suitable method for the preparation of a substantially purified protein or peptide.

[0083] Generally, “purified” will refer to a protein or peptide composition that has been subjected to fractionation to remove various other components, and which composition substantially retains its expressed biological activity. Where

the term “substantially purified” is used, this designation will refer to a composition in which the protein or peptide forms the major component of the composition, such as constituting about 50%, about 60%, about 70%, about 80%, about 90%, about 95% or more of the proteins in the composition.

[0084] Various methods for quantifying the degree of purification of the protein or peptide will be known to those of skill in the art in light of the present disclosure. These include, for example, determining the specific activity of an active fraction, or assessing the amount of polypeptides within a fraction by SDS/PAGE analysis. A preferred method for assessing the purity of a fraction is to calculate the specific activity of the fraction, to compare it to the specific activity of the initial extract, and to thus calculate the degree of purity, herein assessed by a “-fold purification number.” The actual units used to represent the amount of activity will, of course, be dependent upon the particular assay technique chosen to follow the purification and whether or not the expressed protein or peptide exhibits a detectable activity.

Nanoworms and their Preparation

[0085] Upon purification, scFv-ELP assembles predominantly spherical nanostructures that have moderate activity; however, their potency can be significantly enhanced through denaturation and refolding. When optimized, refolding of the scFv domain results in the formation of high-aspect ratio cylindrical micelles (also known as nanoworms). These high aspect ratio particles morphologies exhibit enhanced apoptotic signaling and potency. Refolding can be achieved either in the absence or presence of reducing reagents (including, but not limited to, dithiothreitol, beta mercaptoethanol, or tris carboxyethyl phosphine). Denaturation is accomplished by incubation with chaotropic salts (including, but not limited to, Guanadinium hydrochloride or Urea) at concentrations between 2 and 8 M. To refold the scFv-ELP, chaotropic salts can be removed slowly using dialysis against successive changes of buffers with decreasing concentrations of the chaotropic salt. When the scFv-ELP is again suspended in buffer alone, the refolding process is complete. In addition to the chaotropic salts, dialysis buffers may include, but are not limited to, tris hydrochloride or phosphate buffered saline. The molecular weight cutoff for dialysis can be selected between 3 and 20 kD. Dialysis can occur at temperatures between 4 and 37 Celsius over a period of 1-2 days with successive changes in buffer. After the completion of dialysis, the scFv-ELP retentate may be clarified using ultracentrifugation at 4,000-13,000 RPM. If desired, the scFv-ELP nanoworms may be concentrated by inducing the ELP-mediated phase separation through the addition of 1-4 M sodium chloride at temperatures between 25 and 42 degrees Celsius. If desired, the nanoworms can be sterile filtered through a 0.2 um filter.

Pharmaceutical Compositions

[0086] Pharmaceutical compositions are further provided. The compositions comprise a carrier and ELPs as described herein. The carriers can be one or more of a solid support or a pharmaceutically acceptable carrier. In one aspect, the compositions are formulated with one or more pharmaceutically acceptable excipients, diluents, carriers and/or adjuvants. In addition, embodiments of the compositions include ELPs, formulated with one or more pharmaceutically acceptable auxiliary substances.

[0087] The invention provides pharmaceutical formulations in which the one or more of an isolated polypeptide of

the invention, an isolated polynucleotide of the invention, a vector of the invention, an isolated host cell of the invention, or an antibody of the invention can be formulated into preparations for injection in accordance with the invention by dissolving, suspending or emulsifying them in an aqueous or nonaqueous solvent, such as vegetable or other similar oils, synthetic aliphatic acid glycerides, esters of higher aliphatic acids or propylene glycol; and if desired, with conventional additives such as solubilizers, isotonic agents, suspending agents, emulsifying agents, stabilizers and preservatives or other antimicrobial agents. A non-limiting example of such is a antimicrobial agent such as other vaccine components such as surface antigens, e.g. a Type IV Pilin protein (see Jurcisek and Bakaletz (2007) J. of Bacteriology 189(10):3868-3875) and antibacterial agents.

[0088] Embodiments of the pharmaceutical formulations of the invention include those in which the ELP is formulated in an injectable composition. Injectable pharmaceutical formulations of the invention are prepared as liquid solutions or suspensions; or as solid forms suitable for solution in, or suspension in, liquid vehicles prior to injection. The preparation may also be emulsified or the active ingredient encapsulated in liposome vehicles in accordance with other embodiments of the pharmaceutical formulations of the invention.

[0089] Suitable excipient vehicles are, for example, water, saline, dextrose, glycerol, ethanol, or the like, and combinations thereof. In addition, if desired, the vehicle may contain minor amounts of auxiliary substances such as wetting or emulsifying agents or pH buffering agents. Methods of preparing such dosage forms are known, or will be apparent upon consideration of this disclosure, to those skilled in the art. See, e.g., Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 17th edition, 1985. The composition or formulation to be administered will, in any event, contain a quantity of the compound adequate to achieve the desired state in the subject being treated.

[0090] Routes of administration applicable to the methods and compositions described herein include intranasal, intramuscular, subcutaneous, intradermal, topical application, intravenous, nasal, oral, inhalation, and other enteral and parenteral routes of administration. Routes of administration may be combined, if desired, or adjusted depending upon the agent and/or the desired effect. An active agent can be administered in a single dose or in multiple doses. Embodiments of these methods and routes suitable for delivery, include systemic or localized routes.

Treatment of Disease

[0091] The scFv polypeptides described herein are useful for the specific targeting of scFv-ELPs to cells. One aspect relates to a method for targeting a scFv-ELP to a cell comprising, or alternatively consisting essentially of, or yet further consisting of: contacting the cell with an effective amount of the scFv-ELP polypeptide, wherein the scFv component of the scFv-ELP binds to a cellular component of the cell. The contacting can be to a cell in vitro or in vivo. In one embodiment, the scFv component binds to a cell surface receptor of the cell. In further embodiment, the scFv component binds to an intercellular receptor or a cellular component found on the surface or inside of the cell. These polypeptides may be used to target cell populations with a specific component by using a scFv that recognizes the specific component. The targeting can facilitate drug delivery by conjugating a drug to the scFv-ELP or facilitate cellular signaling by ago-

nizing or antagonizing a cellular receptor. The cellular signaling may induce a specific cellular response. In the case of CD20, multivalent binding of the anti-CD20 to the cell-surface receptor induces apoptosis of the cell. Accordingly, one aspect relates to a method for inducing apoptosis of a CD20+ cell comprising contacting the cell with an effective amount of the scFv-ELP polypeptide wherein the scFv component comprises, or alternatively consists essentially of or yet further consists of the single chain variable region from the anti-CD20 antibody. In a related embodiment, the cell is a malignant B-cell. In another aspect, the compositions are useful to treat a CD20-related disease or disorder, e.g., a CD20-expressing cancer, by administering to a patient in need of such treatment the polypeptide of any one of the compositions of this invention. In one aspect, the CD20-expressing cancer is non-Hodgkin lymphoma.

[0092] In some embodiments of the disclosure, the entire anti-CD20 antibody is linked to the ELP. Linking the entire antibody to the ELP may provide additional benefits to therapeutic applications utilizing the anti-CD20 antibody alone. For example, the ELP-conjugated CD20 antibody may provide a more efficient mechanism for crosslinking the antibody. Since activation of apoptosis in CD20+ cells requires multivalent binding of the CD20 cell surface antigen, the ELP-conjugated anti-CD20 antibody may provide more efficient activation of apoptosis. In one aspect, a portion of the anti-CD20 antibody is used.

[0093] A further aspect relates to a method for treating a CD20 expressing cancer, comprising administering to a patient in need of such treatment the scFv-ELP polypeptide wherein the scFv component comprises, or alternatively consists essentially of or yet further consists of the single chain variable region from the anti-CD20 antibody or a polynucleotide encoding such polypeptide. One example of a CD20 expressing cancer is non-Hodgkin lymphoma. Also provided are kits for treating a CD20 expressing cancer in a subject, comprising the scFv-ELP polypeptide wherein the scFv component comprises the single chain variable region from the anti-CD20 antibody or a polynucleotide encoding such polypeptide, and optionally, instructions for use.

Combination Treatments

[0094] Administration of the therapeutic agent or substance of the present invention to a patient will follow general protocols for the administration of that particular secondary therapy, taking into account the toxicity, if any, of the treatment. It is expected that the treatment cycles would be repeated as necessary. It also is contemplated that various standard therapies, as well as surgical intervention, may be applied in combination with the described therapy.

Kits

[0095] Also provided is a kit for treating a CD20 expressing cancer in a subject or for conducting a screen, as outlined below, containing an ELP-CD20 polypeptide and/or polynucleotide, and optionally, instructions for use.

Screens

[0096] The present invention also provides methods to identify leads and methods for inducing apoptosis or treating CD20+ cancers and/or disorders. In one aspect, the screen identifies lead compounds or biologics agents that mimic the ELP fusion polypeptide identified above and which are useful

to treat these disorders or to treat or ameliorate the symptoms associated with the disorders. Test substances for screening can come from any source. They can be libraries of natural products, combinatorial chemical libraries, biological products made by recombinant libraries, etc. The source of the test substances is not critical to the invention. The present invention provides means for screening compounds and compositions which may previously have been overlooked in other screening schemes.

[0097] To practice the screen or assay in vitro, suitable cell cultures or tissue cultures are first provided. The cell can be a cultured cell or a genetically modified cell which differentially expresses the receptor and/or receptor complex. Alternatively, the cells can be from a tissue culture. The cells are cultured under conditions (temperature, growth or culture medium and gas (CO₂)) and for an appropriate amount of time to attain exponential proliferation without density dependent constraints. It also is desirable to maintain an additional separate cell culture; one which does not receive the agent being tested as a control.

[0098] As is apparent to one of skill in the art, suitable cells may be cultured in microtiter plates and several agents may be assayed at the same time by noting genotypic changes, phenotypic changes and/or cell death.

[0099] When the agent is a composition other than a DNA or RNA nucleic acid molecule, the suitable conditions may be by directly added to the cell culture or added to culture medium for addition. As is apparent to those skilled in the art, an "effective" amount must be added which can be empirically determined.

[0100] The screen involves contacting the agent with a test cell expressing the complex and then assaying the cell its ability to provide a biological response similar to the ELP fusions described herein. In yet another aspect, the test cell or tissue sample is isolated from the subject to be treated and one or more potential agents are screened to determine the optimal therapeutic and/or course of treatment for that individual patient. A control wherein the ELP fusion of this invention is applied can be performed and the test agent can be compared to the control.

[0101] For the purposes of this invention, an "agent" is intended to include, but not be limited to a biological or chemical compound such as a simple or complex organic or inorganic molecule, a peptide, a protein or an oligonucleotide. A vast array of compounds can be synthesized, for example oligomers, such as oligopeptides and oligonucleotides, and synthetic organic compounds based on various core structures, and these are also included in the term "agent". In addition, various natural sources can provide compounds for screening, such as plant or animal extracts, and the like. It should be understood, although not always explicitly stated that the agent is used alone or in combination with another agent, having the same or different biological activity as the agents identified by the inventive screen. The agents and methods also are intended to be combined with other therapies. They can be administered concurrently or sequentially.

[0102] Use of the screen in an animal such as a rat or mouse, the method provides a convenient animal model system which can be used prior to clinical testing of the therapeutic agent or alternatively, for lead optimization. In this system, a candidate agent is a potential drug, and may therefore be suitable for further development, if the agent binds the receptor or receptor complex each as compared to untreated, ani-

mal expressing the receptor and/or complex. It also can be useful to have a separate negative control group of cells or animals which are healthy and not treated, which provides a further basis for comparison.

EXAMPLES

Example 1

Characterization of scFv-ELP Fusion Proteins

[0103] Cancers including NHL are currently being treated by surgery, radiotherapy, chemotherapy, and more recently immunotherapy. Substantial efforts have been expended to explore these modalities, but more innovative ideas are needed to gain ground against tumor resistance. To develop a new modality based on cancer nanomedicine, Applicants have invented novel methods that combine cell expression

non-specific in comparison to the CD20-mediated direct induction of apoptosis. The scFv-ELP nanomedicines, therefore present a unique opportunity to shift the mechanism of cell-killing to direct induction of apoptosis; (iv) the potential for local deposition of heat to target the hyper-activation of scFv-ELPs predominantly to tumors; and (v) ELP nanoparticles designed to phase separate under the skin, are a new approach to form slow-release depots that can extend the interval between dosing.

[0104] The fusions in Table 1 have been cloned and expressed. The scFv ELPs were purified using inverse temperature cycling. The scFv fusion have similar phase behavior to ELP. Applicants have observed that scFv-ELPs promote nanoparticle assembly independent of temperature. The scFv-A192 nanoparticles have transition temperatures above physiological temperature; therefore they are expected to remain soluble in the body unless the tissue is deliberately heated (FIG. 1).

TABLE 1

Label	Peptide sequence	*ELP MW (kD)	Target behavior in body	**Assembly Temp. (° C.)	***Hydrodynamic Radius at 36° C., R_h = (nm)
V96	G(VPGVG) ₉₆ Y (SEQ ID NO: 10)	39.5	depot, control	30	n.d
192	G(VPGAG) ₁₉₂ Y (SEQ ID NO: 11)	73.5	soluble, control	55	6
scAB-V96	anti-CD20 scAB-G(VPGVG) ₉₆ Y (G(VPGVG) ₉₆ Y disclosed as SEQ ID NO: 10)	65.3	Depot	n.d	n.d
scAB-A192	anti-CD20 scAB G(VPGAG) ₁₉₂ Y (G(VPGAG) ₁₉₂ Y disclosed as SEQ ID NO: 11)	99.3	soluble, thermally triggered	41	23

*Molecular weight estimated for expressed ELP gene product.

**Assembly temperature determined using optical density at 350 nm on a temperature gradient of 1° C. min⁻¹. n.d. not yet determined

***Radii determined using dynamic light scattering at 25 μM ELP in phosphate buffered saline.

biology, bioresponsive peptides, and self-assembly. The nanoparticles are derived from protein polymers that are biologically inspired from a five amino acid motif identified in tropoelastin, a human extracellular matrix protein. These Elastin-Like Polypeptides (ELPs) are ideal for NHL cancer nanomedicines because: (i) the development of a simple, recombinant approach to generate targeted nanomedicines, can become a platform for developing antibody nanomedicines targeted at other receptors; (ii) due to their low MW and lack of an Fc domain, scFv fragments are rapidly cleared by the kidney and have short circulation times. Because this approach will generate significantly higher molecular weight scFv fusion proteins and nanoparticles, these reagents will have more favorable pharmacokinetics in vivo; (iii) for Rituximab, the Fc domain is responsible for complement and antibody dependent cytotoxicity, both of which are relatively

[0105] FIG. 1 shows phase diagrams of ELP and scFv ELP fusions including ELP A192 (FIG. 1A) and scFv A192 (FIG. 1B). The linear regression depicted in FIG. 1C shows a concentration dependent change in transition temperature.

Protein Polymer Therapeutics for Non-Hodgkins Lymphoma Therapy

[0106] Non-Hodgkin's lymphomas are usually characterized by the uncontrolled replication of malignant B-cells. B-cell surface receptor, CD20, is an established surface marker which has been targeted using antibody therapeutics (for example, Rituximab). Antibody-mediated crosslinking of CD20 induces colocalization to lipid rafts and apoptotic signaling. Utilizing the CD20 crosslinking phenomenon, Applicants have genetically fused a single chain antibody variable fragment (scFv) of the CD20 IgG to environmentally

responsive biopolymers called Elastin like polypeptides (ELPs). The resulting fusion proteins are: i) thermally sensitive; ii) target CD20; and iii) induce malignant B-cell apoptosis; and unexpectedly assemble uniform, spherical nanoparticles.

Cloning of scFv-ELP Fusions

[0107] The scFv sequence was ordered from IDT in a pIDTsmart vector. pIDTsmart vector is double digested with NdeI (NEB) and BamHI (NEB) and the scFv sequence purified using agarose gel extraction. The purified sequence is then inserted into a pET25b(+) plasmid which is digested similarly. The insert and the plasmid are ligated with DNA ligase (NEB). The pET25b(+) plasmid with the scFv insert is again double digested with BseRI and XbaI and ligated to a pET25b(+) plasmid containing the desired ELP sequence. The ligated plasmid is sequence confirmed and transformed into Origami B cells (Novagen) and plated on agar plate with ampicillin. All colonies obtained are screened for expression of required protein and DMSO stocks made. The cloning scheme is depicted in FIG. 13.

[0108] Crosslinking of surface bound CD20 by a secondary antibody promotes translocation of the cross-linked complex to lipid rafts causing downstream signaling of apoptotic pathways (FIG. 2). The scFv fragment of anti-CD20 was genetically fused to the N-terminus of ELP (FIG. 3). The ELP was fused to the variable light chain of the scFv. The plasmid containing the fusion was transformed into *E. coli* and expressed. The scFv A192 can be purified using inverse temperature cycling (ITC) (FIG. 4A) and assembles particles with hydrodynamic radius of ~32 nm whereas A192 is ~6 nm (FIG. 4B). Uranyl Acetate contrast enhanced transmission electron microscopy (TEM) images of scFv A192 reveals nanoparticles, which are 51.7 ± 12.4 nm wide (FIG. 5A) and Cryo TEM images of scFv A192 show monodisperse particles of 48.1 ± 11.8 nm in diameter (FIG. 5B). Fusion of scFv to the ELP drops the transition temperature ~20° C. The drop in transition temperature correlates with nanoparticle assembly (FIG. 6).

Binding and Activity

[0109] The scFv ELP fusion recognizes surface CD20. Rhodamine (RHD) labeled scFv A192 fusions bind CD20+ Raji cells (FIG. 7A-D). scFv A192 forms distinct punctate bodies on the cell surface (FIG. 7C). CD20- CEM cells are not stained by scFv A192 (FIG. 7E-H). scFv A192 induces cell aggregation in CD20+ Raji cells. FIG. 8 also demonstrates the scFv ELP fusion recognition of cell surface CD20 receptors.

[0110] The CD20 antibody abolishes scFv binding (FIG. 9). Raji and CEM cells were treated with unlabeled CD20 antibody and washed. The washed cells were treated with RHD labeled scFv ELP to check CD20 binding. Pretreatment with CD20 antibody abolished scFv binding on Raji cells (FIG. 9A-D). The untreated cells show scFv binding (FIG. 9E-H) suggesting competitive CD20 binding.

[0111] The scFv ELP fusion induce apoptosis in Raji cells. scFv ELP treated cells were stained with Annexin V to detect early stage apoptosis. scFv ELPs induced apoptosis in CD20+ Raji cells (FIG. 10, left panel) and not in CD20- CEM cells (FIG. 10, right panel).

[0112] scFv ELP fusion selectively kill Raji cells. MTS assay performed on Raji and CEM cells show selective killing on Raji cells (FIG. 11). The selectivity illustrates CD20 targeting. It is worth noting the high IC50 value of the fusion. This can be attributed to self-assembly of scFv particles initiated by the scFv tag. The assembly reduces the number of available active scFv tag causing the increase in IC50.

[0113] scFv ELP also induce Raji cell apoptosis. As shown in FIG. 12, Annexin V (ANX) staining show induction of apoptosis in CD20 +ve Raji cells (FIGS. 12A-C) and not in CD20 -ve CEM cells (FIGS. 12D-F).

[0114] ELPs are versatile polymers which can be modified by simple genetic modification. The ELP serves as a purification tag similar to Poly-histidine, which can be used to display single chain antibody fragments. The scFv region promotes assembly of multivalent particles that crosslink surface CD20 and induces apoptosis.

[0115] Multivalent CD20 crosslinking does promote apoptosis in human B-cell lymphomas. Utilizing the versatile ELP polymers Applicants were able to successfully express and purify scFv-ELP fusions which specifically target CD20+ cells. The flexibility of ELPs can be exploited to create an array of multifunctional particles with varied pharmacokinetic properties and potential enhanced biological activity. This crosslinking approach can drastically enhance the clinical activity of available B-cell lymphoma immunotherapy. Further modification of the scFv sequence can lead to development of fusions with better targeting and higher tumor killing efficiencies.

Example No. 2

[0116] In an extension of Experiment No. 1, the following experiments were conducted.

Materials and Methods

[0117] The DNA sequence for anti CD20 scFv (Table 2) was designed and purchased from Integrated DNA Technologies (Coralville, Iowa). Cloning vector (Pet25b(+)), Top10, and Origami B (DE3) were purchased from Novagen (Darmstadt, Germany). Terrific broth (TB) dry powder was purchased from Mo-bio Laboratories (Carlsbad, Calif.). All restriction enzymes were purchased from New England Biolabs (Ipswich, Mass.). SYBR® safe DNA stain, low and high melting point agarose, AnnexinV/PI apoptosis kit and TUNEL staining kit were purchased from Invitrogen (Grand Island, N.Y.). DNA mini prep and DNA purification kits were purchased from Qiagen (Germantown, Md.). Bacteriological grade agar and sodium chloride was purchased from Sigma Aldrich (St. Louis, Mo.). Non-radioactive cell viability MTS assay kit was purchased from Promega (Madison, Wis.). Pre-cast 4-20% SDS PAGE gels were purchased from Lonza (Basel, Switzerland). Raji, CEM, SU-DHL-7, RTXN, and chimeric Lym1 (chLym-1) antibodies were provided to us by Dr. Alan Epstein (USC, Los Angeles, Calif.). Polyclonal goat anti human Fc antibody (2° GAH) was purchased from Thermo Scientific (Rockford, Ill.). Cell culture media, Roswell Park Memorial Institute medium (RPMI 1640), was purchased from Corning (Tewksbury, Mass.). All cells were cultured in RPMI 1640 supplemented with 10% FBS at 37° C. humidified in 5% CO₂.

TABLE 2

Biophysical characteristics of cloned scFv ELP fusions				
ELP Nomenclature	Amino Acid Sequence*	T _t (° C.) [†]	ELP behavior [‡]	Observed ELP MW (Da) [§]
A192	G(VPGAG) ₁₉₂ (SEQ ID NO: 11)	55.1	Soluble	73,472.8
A96I96	G(VPGAG) ₉₆ (VPGIG) _{96Y} (SEQ ID NO: 12)	56.5	Micelle	77,512.5
scFv A192	scFv-G(VPGAG) _{192Y} (disclosed as SEQ ID NO: 11)	42.0	Protein core nanoparticles	99,292.3
scFv A96I96	scFv-G(VPGAG) ₉₆ (VPGIG) _{96Y} (disclosed as SEQ ID NO: 12)	n.a.	n.a.	n.a.

*Gene sequences confirmed by DNA sequencing from N and C terminal.

[†]Transition temperature (T_t) (25 μM, pH 7.4 determined by optical density measurements at 350 nm.

[‡]ELP behavior in PBS.

[§]Molecular weight estimated using SDS-PAGE (n.a.: not available).

[‡]scFv sequence:

'QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIGAIYPNGDTSYN QKFKGKATLTADKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDWYFNVWGAGTTVTVSAGG GSGGGGGSGGGGQIVLSQSPAILASAPGKVTMTCRASSSVSYIHWFFQKPGSSPKPWIYA TSNLASGVPVRFSGSGSTSYSLTISRVEAEDAATYYCQQTSTNPPTFGGGTKLEIKRT' (SEQ ID NO: 13)

Expression and Purification of scFv ELP Fusions

[0118] The anti CD20 scFv was fused to ELPs using restriction enzyme digestion followed by sticky end ligation. The expressed protein was purified from bacterial lysates using inverse temperature cycling. Briefly, the anti-CD20 scFv sequence (756 bp) was purchased in an ampicillin resistant proprietary pIDTsmart™ vector. The scFv sequence was inserted into a pet25b(+) expression vector containing the ELP sequences (Table 2) using restriction enzyme digestion. Sequence confirmed plasmid was transformed into Origami B (DE3) *Escherichia coli* (*E. coli*) using heat shock at 42° C. for 5 mins. The heat shocked bacteria was plated onto an ampicillin (100 μg/1) agar plates and incubated at 37° C. for 15-18 hrs and transformed colonies selected. The selected colonies were grown in 5 ml TB culture media with 100 μg/1 ampicillin for 15-18 hrs at 37° C. The cultures were pelleted at 4,000 rpm for 15 mins and lysed to check for protein expression using SDS-PAGE. A colony with high protein expression was selected and grown out in a 50 ml starter culture with 100 μg/1 ampicillin at 37° C. The bacterial culture was then pelleted and inoculated into 1 liter TB media with 100 μg/1 ampicillin. The cultures were grown for 24 hrs and bacteria suspended in filtered PBS (4 L of culture in 25 ml of PBS) for downstream cell lysis. The bacteria were lysed using ultrasonication to release expressed cytosolic fusion protein and bacterial DNA was complexed out using polyethylenimine (50% w/v PEI) at 12,000 rpm for 15 mins. The supernatant containing the fusion protein was filtered through a 0.2 μm filter before protein purification using inverse temperature cycling (ITC).

Refolding Enhances Efficacy

[0119] The DNA free supernatant was equilibrated to room temperature and ELP phase transition induced by 3M NaCl

(i.e. for 50 ml of supernatant 8 gms of NaCl). The ELP coacervate was spun down at 25° C. for 20 mins at 4000 rpm (HOT SPIN). The supernatant was discarded and the pellet solubilized in cold PBS. The solubilized pellet contains the ELP fusion with insoluble bacterial proteins which were centrifuged out at 4° C. at 12,000 rpm for 15 mins (COLD SPIN). The hot and cold cycle was repeated twice and 6M Guanidine HCl added to perform scFv refolding. Added guanidine is slowly removed by dialysis to promote scFv renaturation using a 20 kD cut off dialysis cassette against cold PBS at 4° C. Dialysis is carried out with a 100:1 sink condition with 4 changes of buffer. A cold spin is performed on the dialyzed protein and a final temperature cycling step performed to ensure complete removal of guanidine. The final protein stock is filtered through a sterile 0.2 μm filter and protein concentration determined using the molar extinction coefficient at 280 nm by:

$$\text{Concentration (M)} = \frac{A_{280} - A_{350}}{\text{MEC}(\epsilon) \times l}$$

Where,

[0120] A₂₈₀: Absorbance at 280 nm

[0121] A₃₅₀: Absorbance at 350 nm

[0122] MEC (ε): Molar extinction coefficient (67,900 M⁻¹C⁻¹)

[0123] l: Path length (cm)

Determination of Purity and Transition Temperature (T_t) of scFv Assemblies

[0124] Purity of the constructs was determined using SDS-PAGE. Briefly, 10-15 μg of protein was added to SDS page

loading buffer and boiled at 95° C. for 5 mins. The sample was then run on 4-20% precast SDS-PAGE gel. After the samples are run the gel is stained using 50 ml of 0.3 M copper (II) chloride solution. The gel was imaged on a Biorad VersaDoc gel imager using white light. The purity of samples was calculated using Image J. Briefly, pictures were imported into ImageJ and converted to 8-bit files. Individual lanes are selected and an intensity plot of each lane made. The peak areas were calculated and the purity was determined using:

$$\% \text{ Purity} = \frac{A_{\text{peak}}}{A_{\text{tot}}} \times 100$$

Where,

[0125] A_{peak} : Area of peak

[0126] A_{tot} : Total area

[0127] The Tt is used to understand the effect of scFv fusion on the ELP. The Tt of the fusions was determined using optical density measurements at 350 nm. Briefly, increasing concentrations of constructs were added to 300 μ l Beckman Coulter Tm microcells (Brea, Calif.) and the temperature was ramped at a rate of 1° C./min. The optical density was plotted as a function of temperature, and the maximum first derivative of this curve was defined as the Tt. The Tt for all samples was determined in PBS.

Light Scattering Analysis of scFv ELP Fusions

[0128] Light scattering was used to determine stability and assembly properties of the scFv ELP fusions. To prevent detection of artifacts, all buffers used were sterile filtered using 0.45 μ m filter. Dynamic light scattering (DLS) was used to determine the hydrodynamic radius (R_h), temperature stability and the polydispersity of the protein in solution. Briefly, increasing concentrations of scFv ELP were pipetted into a 384-well clear bottom plate and read on a Wyatt DynaPro plate reader (Santa Barbara, Calif.) using a 830 nm laser and a 1° C./min temperature ramp from 20° C.-45° C.

[0129] Multi angle light scattering (MALS) was used to determine the R_g , molecular weight, and coordination number of the scFv fusions. The fusions were analyzed using tandem size exclusion chromatography and multi angle light scattering (SEC-MALS). Briefly, 250 μ g of constructs were injected onto a Shodex® size exclusion column using sterile filtered PBS at 0.5 ml/min. The column eluents were analyzed on a Wyatt Helios system (Santa Barbara, Calif.) and the data fit to a Debye plot to determine the R_g and the molecular weight. The coordination number for the assemblies was determined by dividing the absolute molecular weight (M_{abs}) by the calculated monomeric scFv ELP molecular weight. The R_g/R_h ratio was used to determine the morphology of the scFv ELP fusion.

Electron Microscopy of scFv ELP Fusion

[0130] Cryogenic TEM (cryoTEM) and contrast stain TEM (conTEM) were performed to determine morphology in the presence and absence of aqueous buffer. Briefly, cryoTEM specimens were prepared using an FEI Vitrobot (Hillsboro, Oreg.). ELP solutions were kept in an ice bath (4° C.) before processing and then raised to 37° C. immediately prior to blotting. Six μ l of sample was pipetted onto a TEM grid coated with a lacey carbon film (LC325-Cu, Electron Microscopy Sciences). The specimen was then blotted under 95% humidity, immediately transferred into liquid ethane, and

stored in liquid nitrogen environment. Micrographs were acquired using FEI Tecnai 12 TWIN TEM equipped with 16 bit 2K×2K FEI eagle bottom mount camera (Hillsboro, Oreg.). All cryoTEM images were acquired at an accelerating voltage of 100 kV. Images were analyzed using ImageJ (NIH, USA).

Secondary Structure Determination Using Circular Dichroism (CD)

[0131] CD was performed to determine the secondary structure of the scFv constructs. The constructs were run on a Jasco J-815 CD spectrometer (Easton, Md.) using a quartz cuvette (path length~1 mm) The ellipticity was monitored from 185-250 nm and the spectra of buffer subtracted post run. All the constructs were prepared in filtered diH₂O. Deconvolution was performed under the assumption that the observed molar ellipticity $[\theta]$ is a weighted linear sum of the ellipticity for known secondary structures. The data was fit using nonlinear regression on Microsoft Excel using

$$\theta = \sum \theta_{\text{std}} C_{\text{std}}$$

Where,

[0132] θ : Observed ellipticity

[0133] θ_{std} : Ellipticity of standard

[0134] C_{std} : Fraction of standard

Antibody Core Protein Polymer 'Nanoworms' (ACPPNs) Design and Purification

[0135] In order to exploit the CD20 induced tumoricidal effect, recombinant scFv was fused (FIG. 14A, Table 2) with elastin like polypeptide (ELP). ELPs are hydrophilic biopolymers with pentameric repeats of $[VPGXG]_n$, (SEQ ID NO: 6) where X can be any amino acid and n is an integer of at least 1. ELPs undergo a characteristic reversible phase transition above a certain critical temperature (LCST) (Urry, D. et al. (1997) J Phys Chem B 101:11007-11028. The recombinant scFv fusion was designed with the RTXN scFv fragment fused to the N-terminus of a large molecular weight (MW) ELP (FIG. 14B). The large MW ELPs were chosen for several reasons. ELP tags enable quick and efficient purification via inverse temperature cycling (ITC) and serve as biodegradable carriers for scFvs, improving their circulation time. Genetic engineering and biological synthesis allows for accurate control over length and sequence, and by designing the construct as a direct fusion of the scFv and ELP, chemical conjugation is avoided. Additionally, the bacterial expression of these fusions allows for a commercially viable product.

[0136] Utilizing the ELP tag, the scFv fusions were purified from bacterial lysate using ITC. The purity determined through Coomassie stained SDS-PAGE was 91.4±1.3%. The yield of the fusion was estimated to be 20-30 mg/L of bacterial culture. The purified fusion retained its phase transitioning property but transitioned at a lower temperature due to the conjugation of the scFv fragment. The high absorbance at 350 nm suggests formation of large scFv A192 assemblies even at room temperature. The scFv A192 fusion transitions at ~41° C. when compared to the plain A192 ELP at ~55° C. DLS confirmed formation of assemblies with a R_h of 85.7±16.5 nm. The R_h for unmodified A192 is 6.7±0.2 nm, suggesting that the fusion assembled particles. The assembly of particles could be due to the scFv fusion and it is likely that the scFv is forming the core of these particles.

scFv Renaturation Stabilizes Secondary Structure and Forms ACPNs

[0137] To address this unexpected particle assembly, 6M guanidine was added to disrupt these structures. The secondary structure and particle parameters of scFv-A192 were compared before (raw) and after renaturation (refolded). Using circular dichroism, the secondary structure of raw scFv-A192 particles showed no characteristic spectra, but deconvolution revealed a mixture of secondary structures. The change in refolded secondary structure for ACPNs was confirmed by a substantial reduction in β -turn content. This suggests a decrease in ELP-mediated aggregation. The ACPNs are stable to temperatures below 41° C. and do not phase separate under normothermic conditions (−37° C.), which makes them suitable for therapeutic evaluation.

[0138] Microscopy of raw protein, utilizing cryoTEM, confirmed monodisperse spherical particles in solution with a diameter of 48.1±11.8 nm. In contrast, the refolded nanoparticles showed a major population of high aspect ratio nanoparticles with lengths of 56.2±15.9 nm and widths of 17.9±3.5 nm. A minor population of spherical particles with a diameter of 27.4±7.5 nm was also observed. The spherical particles may also be nanoworms with their long axes parallel to the electron beam. Based on their size, composition, and morphology, these refolded nanoparticles are defined as Antibody Core Protein Polymer Nanoworms (ACPPNs).

[0139] The particle assemblies were compared independently using multi angle light scattering (MALS). MALS analysis performed on raw scFv-A192 confirmed assembly of particles with an absolute molecular weight (M_{abs}) of 25,490 kD. The M_{abs} confirmed particle assembly with each particle made up of ~250 scFv-A192 monomers with an R_g of 47.7±0.1 nm. In fact, the refolded particles showed a significant reduction in M_{abs} giving rise to a mixture of 8,372 kD and 8,073 kD particles. The reduction in M_{abs} translates to about 80 scFv A192 monomers making up these particles. The two populations have similar M_{abs} but with varying radii of gyration of 45.2±0.1 and 33.7±0.1 nm respectively. Interestingly, the two particle populations appear as a single population with an R_h of 65.3±15.5 nm using DLS. The R_g/R_h ratios were used to determine the morphology changes due to refolding. The raw scFv-A192 R_g/R_h of 0.56 shifted as high as 0.7 after refolding. The low R_g/R_h value for the scFv-A192 (<0.7 for polymeric micelles) is consistent with the assembly of spherical particles with a densely packed core. In contrast, the refolded scFv-A192 consists of two populations with apparently different shapes and packing densities. Data obtained through MALS experiments is consistent with Applicants' cryoTEM observations, but an accurate measurement of R_h for the subpopulations was not possible due to challenges with separating the two particles.

In Vitro CD20 Recognition Using Laser Confocal Microscopy

[0140] CD20 recognition was tested in CD20+ and CD20− cells. For CD20+ cells, Burkitt's (Raji) and diffuse large B-cell lymphoma (SU-DHL-7) cell lines were evaluated against ACPNs. A CD20− T-acute lymphoblastic leukemia (T-ALL), CEM, was used as a CD20-control. scFv CD20 recognition was performed using rhodamine (RHD) labeled proteins under laser assisted confocal microscopy. Briefly, 50 μ g of RHD labeled scFv ELP and RTXN were added to 1 ml of 2×10⁵ cells suspended in 1% BSA DPBS. The cells were incubated with the protein for 15 mins at room temperature

with occasional agitation. After incubation, cells were transferred to 3 ml test tubes and centrifuged at 750 rpm for 5 mins to remove unbound proteins. The cell pellets were washed twice with DPBS and suspended in 100 μ l 1% BSA DPBS. The cells were mounted onto glass slides and observed under a Zeiss LSM510 confocal microscope with a 543 nm green excitation laser. For RTXN competition studies, the cells were incubated with 1 mg of unlabeled antibody for 15 mins and washed. Prior to incubation with RHD labeled scFv constructs for a further 15 mins. GAH crosslinked RTXN was imaged in a similar fashion to RHD RTXN treated cells but 10 μ g of 2° GAH was added to the washed cells and incubated for a further 15 mins to induce crosslinking. After the incubation, the cells were washed and imaged. Images were analyzed using Image J (NIH, USA).

Cell Viability Assays

[0141] A formazan based colorimetric assay was used to determine cell viability. Viability assays were performed on CD20+ and CD20− cell lines used in CD20 binding assays. All assays were performed in 5% FBS RPMI 1640 supplemented with Pen-Strep. Briefly, 2×10⁴ cells/well were pipetted into 96-well plates and serial dilutions of scFv ELP and RTXN were added in triplicates. RPMI 1640 with appropriate protein dilution was used as blank control. The cells were incubated with the protein for 24 hrs, after which 30 μ l of MTS/PMS was added to determine the number of viable cells. The cells were further incubated for 2 hrs and read at 490 nm using a Biorad benchmark Plus® plate reader (Hercules, Calif.). The % cell viability was calculated and plotted versus protein concentration and viability determined by:

$$\% \text{ Cell viability} = \frac{(A_{\text{treated}} - A_{\text{cont}}) \times 100}{(A_{\text{untreated}} - A_0)}$$

Where,

[0142] A_{treated} : Treated cell absorbance at 490 nm

[0143] A_{cont} : Control absorbance at 490 nm with appropriate protein concentration

[0144] $A_{\text{untreated}}$: Untreated cell absorbance at 490 nm

[0145] A_0 : Control absorbance at 490 nm with no cells

Detection of Apoptosis Through Flow Cytometry

[0146] Induction of apoptosis was determined using early and late stage apoptotic markers. Annexin V (ANXV)/PI staining was used to detect early induction of apoptosis. An antibody against HLA-Dr10 tumor cells, chLym-1, was used as a positive control for direct induction of apoptosis. The chLym-1 antibody binds HLA-Dr10 expressing tumor cells inducing cell lysis. Briefly, 2×10⁵ cells in 10% FBS RPMI 1640 supplemented with Pen-Strep were added to each well in a 12 well plate. The cells were incubated with equivalent scFv concentrations of scFv ELP, RTXN, RTXN+2° GAH and chLym-1 at 37° C. with humidified 5% CO₂ for 18 hrs. For ANXV+ and PI+ compensation controls, cells were treated with 50 μ g of paclitaxel. For 2° GAH mediated crosslinking the cells were incubated with RTXN for 30 mins and resuspended in fresh cell culture media. After washing, 100 μ g of 2° GAH was added the cells and incubated for 18 hrs. After incubation the cells were pelleted, washed twice with PBS, and suspended in 100 μ l ANXV staining buffer.

The cells were stained with ANXV and PI as per the manufacturer's instructions i.e. 5 μ l of Alexa Fluor® 488-ANXV stock and 1 μ l of 5-fold diluted PI stock were added to the cell and incubated for 15 mins. The volume of cells was made up to 500 μ l with ANXV binding buffer and analyzed on an Attune™ acoustic focusing flow cytometer (Life technologies, Grand Island, N.Y.). The data were collected as .fcs files and analyzed on Flowjo.

[0147] Late stage apoptosis was detected using terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL). The labeling was performed as per the manufacturer's protocol. Briefly, 2×10^6 cells in 10% FBS RPMI 1640 supplemented with Pen-Strep were added to each well in a 12 well plate. The cells were treated with equivalent scFv concentrations of scFv ELP, RTXN, and RTXN+2° GAH and incubated at 37° C. with humidified 5% CO₂ for 18 hrs. The RTXN crosslinking by 2° GAH (100 μ g) was performed similar to ANXV/PI staining procedure. After incubation the samples were fixed in 1% formaldehyde for 15 mins and dehydrated using 70% ethanol for 5 hrs on ice. The fixed cells were washed, transferred to a BrdUTP labeling buffer and labeled with BrdU overnight at room temperature. After completion of reaction Alexa488 labeled anti-BrdUTP antibody was added and incubated for 2 hrs. PI was added 30 mins before sample analysis and data collected as .fcs files. Analysis of .fcs files was performed on Flowjo.

[0148] Activation of the caspase cascade (Caspase 3,8, & 9) was detected using an FITC labeled cell penetrating irreversible caspase inhibitor, Z-VAD-FMK (carbobenzoxy-valyl-alanyl-aspartyl-fluoromethylketone)²⁹. VAD-FMK binds different caspases with varying affinities²⁹. Briefly, 2×10^5 cells/well in 10% FBS RPMI 1640 supplemented with Penn-Strep were added to 12 well plate and ACPPNs (Fv dose-1.5 mgs/ml) added to appropriate wells. The cells were incubated at 37° C. with humidified 5% CO₂ for 18 hrs. After incubation 2 μ l of 20 mM FITC-VAD-FMK added for 1 ml of culture. The cells were incubated for a further 1 hr at 37° C. with humidified 5% CO₂. The labeled cells were washed with PBS and fixed in 4% formaldehyde and analyzed using flow cytometry. Recorded data was saved as .fcs files and analyzed on Flowjo.

In Vivo Tumor Regression and Biodistribution Studies

[0149] Human Burkitts' lymphoma xenografts (Raji) were used to determine in vivo efficacy of scFv constructs. All procedures performed were in accordance to the university approved IACUC protocol. Briefly, Athymic nude mice were irradiated using an X-ray irradiator (400 rads) to lower their NK cell population and allowed to recover for 24 hrs. After recovery, a 200 μ l inoculum of 5×10^6 Raji cells and 10^5 human fetal fibroblasts, used to support early tumor growth, were implanted subcutaneously on the right flank of the mouse. The mice were divided into 3 treatment groups (n=5): PBS, RTXN (1.7 mgs/dose) and ACPPNs (scFv A192, 2.5 mgs/dose). RTXN and ACPPNs were dosed at an equivalent scFv dose of 600 μ g. Animal dosing was started once all tumors reached 150 mm³ and the total number of doses limited to 8 per mouse. The first two doses were administered on consecutive days and the following six doses given every other day. The weight of the mice and the tumor volumes were monitored and animals were sacrificed after reaching the tumor volume end point (1000 mm³) or due to occurrence of any adverse reactions to treatment. Organs from sacrificed animals were harvested and fixed in zinc formalin for 18 hrs and dehydrated in 70% alcohol for 24 hrs before paraffin

embedding. After dehydration the dry weights of the liver, spleen, and tumor recorded. After paraffin embedding, fine 5 μ m slices of the organs were stained with Hematoxylin and eosin (H & E) and studied for histological changes. The tumor volume for this study was calculated using the following formula:

$$\text{Tumor volume} = \frac{\pi}{6}(w^2 \times l)$$

Where,

[0150] $\pi=3.14$.

[0151] w=Measured width of tumor.

[0152] l=Measured length of tumor.

[0153] In vivo biodistribution studies were performed using RHD labeled scFv A192 in Raji xenografted mice (n=3). A therapeutic dose of scFv A192 (2.5 mgs) was administered to the animals and the animals sacrificed after 8 hrs. The organs of the animals were harvested and fixed in zinc formalin for 18 hrs and dehydrated in 70% alcohol for a further 24 hrs prior to paraffin embedding. Paraffin was removed and the sections permeabilized with 10% SDS. The nuclei were stained by incubation in a 1:1000 dilution of DAPI for 1 hr. After incubation, the sections were washed with 1% BSA PBS and slides prepared with antifade reagent. The slides were dried overnight and imaged under a Zeiss LSM510 laser confocal microscope. A 543 nm and 790 nm excitation lasers were used to image RHD and DAPI, respectively. All images were processed on ImageJ.

ACPPNs Target Recognition and In Vitro Efficacy

[0154] RHD labeled RTXN and ACPPNs successfully recognized two CD20+B-cell lymphomas (FIG. 16B (i-iii, vii-xi)). RTXN efficiently bound CD20 with equal distribution of CD20 on the cell surface (FIG. 16A (i-iii, vii-xi)). On addition of 2° GAH the surface bound RTXN showed a speckled or punctate pattern on the cell surface due to translocation of crosslinked RTXN into lipid rafts (FIG. 16A (iv-vi, x-xii)). ACPPNs also bound CD20 forming a punctate pattern similar in appearance to crosslinked RTXN. The binding of ACPPNs can be blocked by pretreating both CD20+ cells with unlabeled RTXN suggesting competitive binding of cell surface CD20. (FIG. 16B (vii-xi, vii-xi)). Conversely, RTXN and ACPPNs showed minimal binding to CD20- CEM cells. Unmodified A192 also showed minimal binding of Raji and SU-DHL-7 cells.

[0155] Preliminary experiments with trypan blue exclusion show a significant increase in trypan positive cells when CD20+B-cells, Raji, and SU-DHL-7, were treated with increasing concentration of ACPPNs (FIG. 17A). A formazan (MTS/PMS) based colorimetric assay confirmed a concentration dependent reduction in cell viability of CD20+ cells with an IC₅₀ of 32 μ M and 41 μ M in Raji and SU-DHL-7 cells, respectively (FIG. 17B). In contrast, RTXN treatment showed minimal changes in cell viability of Raji cells. RTXN treatment reduced cell viability by 20-25% in Raji cells irrespective of concentration used and therefore an IC₅₀ could not be calculated. Interestingly RTXN showed potent concentration dependent reduction in viability of SU-DHL-7 cells with an IC₅₀ of 4.8 μ M. CD20- cells, CEM, did not respond

to RTXN treatment but showed a slight decrease in viability at higher ACPPN concentrations. The IC₅₀ of ACPPNs for CEM cells was 294 μ M.

[0156] Induction of early and late stage apoptosis was detected by ANXV/PI staining and TUNEL, respectively. ACPPN treatment (scFv dose-1.5 mg/ml) significantly enhanced induction of early apoptosis in both CD20+ cell lines as detected using ANXV/PI staining. RTXN dosed at the same scFv concentration showed variable induction of apoptosis in CD20+ cell lines with Raji cells responding better than SU-DHL-7 cells (FIG. 17C). On crosslinking RTXN with 2° GAH, both cell lines showed an increase in early apoptosis. Since ACPPNs induce apoptosis on binding, a positive control antibody, Chimeric lym1 (chLym-1), with similar mechanism of action was used. The chLym-1 control is an anti HLA-Dr10 antibody which is an effective inducer of apoptosis on direct cell binding (Zhang, N. et al. (2007) Cancer Biother Radiopharm 22: 342-356 and Tobin, E. et al. Leuk Lymphoma 48: 944-956) (FIG. 17C). Treatment with an equi-scFv dose of chLym-1 performed better than plain ACPPNs in Raji cells but was less effective in SU-DHL-7 cells. The variable response could be due to a lower expression of surface HLA-dr10 on SU-DHL-7 cells (FIG. 17C) (Rimsza, L. M. et al. (2004) Blood 103: 4251-4258. Unlike chLym-1, ACPPNs were equally potent in both cell lines. It is interesting to note that results for RTXN treated SU-DHL-7 cells from the formazan based viability assay are contrary to findings from ANXV/PI staining CEM cells treated with ACPPNs showed minimal induction of apoptosis and hence were not evaluated further (FIG. 17C).

[0157] TUNEL staining was used to determine the induction of late apoptosis because ANXV/PI staining is known to detect early apoptosis. All proteins were compared with an equivalent Fv dose of 2.5 mg/ml. ACPPN treatment significantly enhances apoptosis compared to plain RTXN (Unpaired 2 tail t-test, $\alpha=0.05$, $P=0.006^*$, $P=0.006^{**}$) in both CD20+ cell lines (FIG. 17D). The efficacy of RTXN can be enhanced to the same extent as ACPPNs by crosslinking with 2° GAH (FIG. 17D). Subsequently, the activation of apoptotic caspase cascade was confirmed using FITC-VAD-FMK (FIGS. 17E-F). A substantial increase in the FITC signal was observed after ACPPN treatment in both Raji and SU-DHL-7 cells. The activation of the caspase cascade by ACPPNs is similar to hypercrosslinked RTXN. Zhang, N. et al. (2005) Clinical Cancer Research, Vol. 11:5971-5980. Hence the ACPPNs are effective inducers of apoptosis in both B-cell lymphoma cell lines and outperform RTXN in vitro.

ACPPNs Biodistribution and Tumor Regression

[0158] RHD labeled ACPPNs injected in Raji xenografted athymic nude mice (n=3) showed accumulation in various organs (FIG. 18A-H). RHD signal was seen in the liver (FIG. 18A, E), spleen (FIG. 18B, F), tumor (FIG. 18C, G) and kidney (FIG. 18D, H), and, minimal accumulation was observed in the heart and lungs. Tumor regression studies were performed in mice with Raji xenografts implanted in the right flank of athymic nude mice (n=5/group). The mice were dosed every other day until 8 doses were administered, and tumor volume was monitored until the tumor volume endpoint (1000 mm³) was reached. ACPPNs treatment significantly retarded tumor growth compared to plain RTXN and PBS groups (FIG. 18I). Repeated measures 1-way ANOVA performed on the mean tumor volumes showed a significant difference between ACPPNs, RTXN, and PBS treated group

($P=0.0011$). Tukey post hoc analysis show a statistically significant difference between ACPPNs, RTXN ($P=0.0015$), and PBS ($P=0.018$) treatment. Tumor volumes of RTXN and PBS showed no statistically significant difference ($P=0.148$). ACPPNs treatment significantly improved survival when compared to RTXN and PBS treatment groups ($P=0.013$, FIG. 18J). The median survival times for ACPPN, RTXN, and PBS were 33, 19 and 25 days, respectively. The administered doses were adequately tolerated but produced a weight loss (~20%) observed in ACPPNs group after the first dose. The weight was recovered by day 13 with no causalities to treatment.

[0159] The dry weight of the organs in the three groups did not change appreciably except for the spleen. A slight increase in dry spleen weight was observed in RTXN and ACPPNs groups when compared to the PBS treatment group (Table 3). Similarly, major organs collected showed no observable histological changes in the three groups except for the tumor. The tumors in the RTXN and ACPPNs treatment groups showed similar histology with prominent necrotic regions compared to that seen in the PBS groups.

TABLE 3

Dry organ weights from tumor regression study			
Group	Liver (μ g)	Spleen (μ g)	Tumor (μ g)
PBS	1033.7 $\pm$ 209.2	91.8 $\pm$ 14.7	551.3 $\pm$ 195.4
RTXN	1039.3 $\pm$ 167.4	145.0 $\pm$ 49.9	474.0 $\pm$ 81.4
ACPPNWs	964.7 $\pm$ 75.9	118.2 $\pm$ 41.8	451.0 $\pm$ 104.1

Experimental Discussion

[0160] Utilizing simple genetic engineering, Applicants constructed scFv based therapeutics which were successfully purified from bacterial lysates using the ELPs as the purification tag. To the best of Applicants' knowledge, this is the first demonstration of ELPs being used as a purification tag for bacterially expressed recombinant scFv. The formation of large spherical particles by 'raw' protein could be due to (1) high salt concentration used to induce ELP phase transition, which could contribute to scFv denaturation leading to assembly or (2) recombinant scFv multimerization forming dimeric, trimeric, and even hexameric molecules (32,33) which could trigger particle assembly with a multimeric scFv core. The particle formation was reduced by guanidine renaturation but the process led to the formation of recombinant ACPPNs which efficiently targeted CD20 expressed on the surface of B-cells lymphomas. The formation of 'worms' was confirmed using cryoTEM which showed particles of 56.2 $\pm$ 15.9 nm in length. The worms still assemble with a scFv core but with a lower M_{abs} and relatively constant R_g . Due a lower mass distributed in the same volume after refolding Applicants hypothesize that the scFv core may be more accessible, allowing for CD20 recognition. The small population with a lower diameter could have a less accessible core and may not contribute to the molecules efficacy.

[0161] In vitro activity was first confirmed by a measuring cell viability which showed selective killing of CD20+ cells albeit at a relatively high IC₅₀ (32 μ M and 41 μ M). Compared to the poor reduction of viability by plain RTXN, however, the IC₅₀ seems acceptable. The reduction in cell viability was confirmed to be due to the induction of apoptosis using two separate techniques targeting different stages of apoptosis.

ACPPNs treatment greatly induced apoptosis (~60%) in both cell lines and outperformed equi-scFv dose RTXN treatment. Also, 2° GAH crosslinked RTXN showed the same efficacy of induction as single agent ACPPNs treatment. An unexpected observation was that RTXN showed potent reduction in SU-DHL-7 viability using formazan based assays but minimal cell staining apoptosis in both apoptosis assays. This contradiction could have arisen due to the 100 fold less cell concentrations used for the experiment.

[0162] The in vitro activity of ACPPNs was successfully translated in vivo using a Raji cell xenograft. ACPPNs treatment showed a significant delay in tumor growth when compared a plain RTXN dosed at the same equivalent scFv dose. A high dose for ACPPNs was chosen based on its activity in vitro. Tumor accumulation of ACPPNs was confirmed by injecting Raji cell xenografted nude mice with RHD labeled reagent. The particles showed high liver, tumor and spleen accumulation (FIG. 19A-H). The high liver and spleen uptake is most likely attributed to the host reticuloendothelial system (Brigger, I., et al. (2002) *Adv Drug Deliv Rev* 54:631-651 and Buzea, C., et al. (2007) *Biointerphases* 2:MR17-71. Kupffer cells in the liver are responsible for nanoparticle clearance (Dobrovolskaia, M. A., et al. (2009) *Nat Nanotechnol* 4:411-414) and hence could be taking up ACPPNs from the circulation. In the spleen, the major RHD signal was present in the marginal zone (MZ) lining the white pulp region (FIG. 19B, F). The marginal zone is mainly populated by phagocytic macrophages and lymphocytes (Martin, F. et al. (2002) *Nat Rev Immunol* 2: 323-335 and Kraal, G. (1992) *Int Rev Cytol* 132:31-74) which play a significant role in filtering and clearing nanoparticles from the body (Aichele, P. et al. (2003) *J of Immunol* 171:1148-1155 and Demoy, M. et al. (1999) *Pharm Res* 16:37-41). Hence the liver and spleen signal could be due to phagocytosis and clearance by effector cells. This finding is consistent with the uptake of nanoparticles with similar size (Moghimi, S. M., et al. (2012) *Annu Rev Pharmacol* 52:481-503). Interestingly, kidney sections also show accumulation of ACPPN particles in the glomerulus confirming the high molecular weight (glomerulus filtration cut off=60,000 kD) of ACPPNs (Meibohm, B., et al. (2012) *J Clin Pharmacol* 52: 54S-62S)

[0163] In conclusion these novel first generation ACPPNs (1) outperform RTXN as a single agent, (2) are biodegradable due to their peptidic nature, (3) are genetically engineered to offer precise control over the sequence, (4) are cheaper to

produce than high molecular weight antibodies, and (5) represent a simple platform to apply to various other scFv targets.

Example 3

Treatment of Subjects with Non-Hodgkin Lymphoma

[0164] Studies are conducted to determine the effects of an amount of recombinant polypeptide comprising scFv ELP fusions in subjects with Non-Hodgkin Lymphoma (NHL). For example, a multicenter, randomized, double-blind, placebo-controlled study is undertaken to evaluate treatment with a weight-based or fixed dose of scFv ELP fusions in subjects with NHL. More specifically, a clinical study is performed to examine the efficacy and safety of a recombinant polypeptide comprising scFv ELP fusions. The scFv ELP is effective to treat and/or prevent NHL.

[0165] It should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification, improvement and variation of the inventions embodied therein herein disclosed may be resorted to by those skilled in the art, and that such modifications, improvements and variations are considered to be within the scope of this invention. The materials, methods, and examples provided here are representative of preferred embodiments, are exemplary, and are not intended as limitations on the scope of the invention.

[0166] The invention has been described broadly and generically herein. Each of the narrower species and subgeneric groupings falling within the generic disclosure also form part of the invention. This includes the generic description of the invention with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein.

[0167] In addition, where features or aspects of the invention are described in terms of Markush groups, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group.

[0168] All publications, patent applications, patents, and other references mentioned herein are expressly incorporated by reference in their entirety, to the same extent as if each were incorporated by reference individually. In case of conflict, the present specification, including definitions, will control.

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Cys	Arg	Ala	Ser	Ser	Ser	Val	Ser	Tyr	Ile	His	Trp	Phe	Gln	Gln	Lys
			165						170					175	
Pro	Gly	Ser	Ser	Pro	Lys	Pro	Trp	Ile	Tyr	Ala	Thr	Ser	Asn	Leu	Ala
		180						185					190		
Ser	Gly	Val	Pro	Val	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Ser	Tyr
	195						200					205			

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Ser	Leu	Thr	Ile	Ser	Arg	Val	Glu	Ala	Glu	Asp	Ala	Ala	Thr	Tyr	Tyr
210						215					220				
Cys	Gln	Gln	Trp	Thr	Ser	Asn	Pro	Pro	Thr	Phe	Gly	Gly	Gly	Thr	Lys
225					230					235					240
Leu	Glu	Ile	Lys	Arg	Thr	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala
				245					250					255	
Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly
			260					265					270		
Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val
		275					280					285			
Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro
	290					295					300				
Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly
305					310					315					320
Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala
				325					330					335	
Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly
			340					345					350		
Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val
		355					360					365			
Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro
	370					375					380				
Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly
385					390					395					400
Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala
				405					410					415	
Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly
			420					425					430		
Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val
		435					440					445			
Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro
	450					455					460				
Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly
465					470					475					480
Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala
				485					490					495	
Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly
			500					505					510		
Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val
		515					520					525			
Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro
	530					535					540				
Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly
545					550					555					560
Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala
				565					570					575	
Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly
			580					585					590		
Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val
		595					600					605			
Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro

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610	615	620
Gly Ala Gly Val Pro	Gly Ala Gly Val Pro	Gly Ala Gly Val Pro Gly
625	630	635 640
Ala Gly Val Pro Gly	Ala Gly Val Pro Gly	Ala Gly Val Pro Gly Ala
645	650	655
Gly Val Pro Gly Ala Gly	Val Pro Gly Ala Gly	Val Pro Gly Ala Gly
660	665	670
Val Pro Gly Ala Gly	Val Pro Gly Ala Gly	Val Pro Gly Ala Gly
675	680	685
Pro Gly Ala Gly Val Pro	Gly Ala Gly Val Pro	Gly Ala Gly Val Pro
690	695	700
Gly Ala Gly Val Pro	Gly Ala Gly Val Pro	Gly Ala Gly Val Pro Gly
705	710	715 720
Ala Gly Val Pro Gly	Ala Gly Val Pro Gly	Ile Gly Val Pro Gly Ile
725	730	735
Gly Val Pro Gly Ile Gly	Val Pro Gly Ile Gly	Val Pro Gly Ile Gly
740	745	750
Val Pro Gly Ile Gly	Val Pro Gly Ile Gly	Val Pro Gly Ile Gly
755	760	765
Pro Gly Ile Gly Val Pro	Gly Ile Gly Val Pro	Gly Ile Gly Val Pro
770	775	780
Gly Ile Gly Val Pro	Gly Ile Gly Val Pro	Gly Ile Gly Val Pro Gly
785	790	795 800
Ile Gly Val Pro Gly	Ile Gly Val Pro Gly	Ile Gly Val Pro Gly Ile
805	810	815
Gly Val Pro Gly Ile Gly	Val Pro Gly Ile Gly	Val Pro Gly Ile Gly
820	825	830
Val Pro Gly Ile Gly	Val Pro Gly Ile Gly	Val Pro Gly Ile Gly
835	840	845
Pro Gly Ile Gly Val Pro	Gly Ile Gly Val Pro	Gly Ile Gly Val Pro
850	855	860
Gly Ile Gly Val Pro	Gly Ile Gly Val Pro	Gly Ile Gly Val Pro Gly
865	870	875 880
Ile Gly Val Pro Gly	Ile Gly Val Pro Gly	Ile Gly Val Pro Gly Ile
885	890	895
Gly Val Pro Gly Ile Gly	Val Pro Gly Ile Gly	Val Pro Gly Ile Gly
900	905	910
Val Pro Gly Ile Gly	Val Pro Gly Ile Gly	Val Pro Gly Ile Gly
915	920	925
Pro Gly Ile Gly Val Pro	Gly Ile Gly Val Pro	Gly Ile Gly Val Pro
930	935	940
Gly Ile Gly Val Pro	Gly Ile Gly Val Pro	Gly Ile Gly Val Pro Gly
945	950	955 960
Ile Gly Val Pro Gly	Ile Gly Val Pro Gly	Ile Gly Val Pro Gly Ile
965	970	975
Gly Val Pro Gly Ile Gly	Val Pro Gly Ile Gly	Val Pro Gly Ile Gly
980	985	990
Val Pro Gly Ile Gly	Val Pro Gly Ile Gly	Val Pro Gly Ile Gly
995	1000	1005
Pro Gly Ile Gly Val Pro	Gly Ile Gly Val Pro	Gly Ile Gly Val
1010	1015	1020

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Pro Gly	Ile Gly Val	Pro Gly	Ile Gly Val	Pro Gly	Ile Gly Val
1025		1030		1035	
Pro Gly	Ile Gly Val	Pro Gly	Ile Gly Val	Pro Gly	Ile Gly Val
1040		1045		1050	
Pro Gly	Ile Gly Val	Pro Gly	Ile Gly Val	Pro Gly	Ile Gly Val
1055		1060		1065	
Pro Gly	Ile Gly Val	Pro Gly	Ile Gly Val	Pro Gly	Ile Gly Val
1070		1075		1080	
Pro Gly	Ile Gly Val	Pro Gly	Ile Gly Val	Pro Gly	Ile Gly Val
1085		1090		1095	
Pro Gly	Ile Gly Val	Pro Gly	Ile Gly Val	Pro Gly	Ile Gly Val
1100		1105		1110	
Pro Gly	Ile Gly Val	Pro Gly	Ile Gly Val	Pro Gly	Ile Gly Val
1115		1120		1125	
Pro Gly	Ile Gly Val	Pro Gly	Ile Gly Val	Pro Gly	Ile Gly Val
1130		1135		1140	
Pro Gly	Ile Gly Val	Pro Gly	Ile Gly Val	Pro Gly	Ile Gly Val
1145		1150		1155	
Pro Gly	Ile Gly Val	Pro Gly	Ile Gly Val	Pro Gly	Ile Gly Val
1160		1165		1170	
Pro Gly	Ile Gly Val	Pro Gly	Ile Gly Val	Pro Gly	Ile Gly Val
1175		1180		1185	
Pro Gly	Ile Gly Val	Pro Gly	Ile Gly Val	Pro Gly	Ile Gly Val
1190		1195		1200	
Pro Gly	Ile Gly Tyr				
1205					

<210> SEQ ID NO 4

<211> LENGTH: 1208

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 4

Met Gly Gln Val Gln Leu Gln Pro Gly Ala Glu Leu Val Lys Pro
1 5 10 15

Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr
20 25 30

Ser Tyr Asn Met His Trp Val Lys Gln Thr Pro Gly Arg Gly Leu Glu
35 40 45

Trp Ile Gly Ala Ile Tyr Pro Gly Asn Gly Asp Thr Ser Tyr Asn Gln
50 55 60

Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr
65 70 75 80

Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr
85 90 95

Tyr Cys Ala Arg Ser Thr Tyr Tyr Gly Gly Asp Trp Tyr Phe Asn Val
100 105 110

Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ala Gly Gly Gly Gly Ser
115 120 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ile Val Leu Ser Gln

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130	135	140
Ser Pro Ala Ile Leu	Ser Ala Ser Pro Gly Glu Lys Val Thr Met Thr	
145	150	155
Cys Arg Ala Ser Ser	Ser Val Ser Tyr Ile His Trp Phe Gln Gln Lys	
	165	170
Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr Ala Thr Ser Asn Leu Ala		175
	180	185
Ser Gly Val Pro Val Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr		190
	195	200
Ser Leu Thr Ile Ser Arg Val Glu Ala Glu Asp Ala Ala Thr Tyr Tyr		205
	210	215
Cys Gln Gln Trp Thr Ser Asn Pro Pro Thr Phe Gly Gly Gly Thr Lys		220
	225	230
Leu Glu Ile Lys Arg Thr Gly Val Pro Gly Ala Gly Val Pro Gly Ala		235
	240	245
Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly		250
	255	260
Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val		265
	270	275
Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro		280
	285	290
Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly		295
	300	305
Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala		310
	315	320
Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly		325
	330	335
Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val		340
	345	350
Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro		355
	360	365
Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly		370
	375	380
Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala		385
	390	395
Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly		400
	405	410
Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val		415
	420	425
Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro		430
	435	440
Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly		445
	450	455
Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala		460
	465	470
Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly		475
	480	485
Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val		490
	495	500
Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro		505
	510	515
Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly		520
	525	530
Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val		535
	540	545

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Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly
545 550 555 560

Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala
565 570 575

Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly
580 585 590

Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val
595 600 605

Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro
610 615 620

Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly
625 630 635 640

Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala
645 650 655

Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly
660 665 670

Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val
675 680 685

Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro
690 695 700

Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly
705 710 715 720

Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala
725 730 735

Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly
740 745 750

Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val
755 760 765

Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro
770 775 780

Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly
785 790 795 800

Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala
805 810 815

Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly
820 825 830

Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val
835 840 845

Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro
850 855 860

Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly
865 870 875 880

Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala
885 890 895

Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly
900 905 910

Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val
915 920 925

Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro
930 935 940

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Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	945
					950					955						960
Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	
				965					970					975		
Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	
			980					985					990			
Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	
		995					1000					1005				
Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val		
	1010					1015					1020					
Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val		
	1025					1030					1035					
Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val		
	1040					1045					1050					
Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val		
	1055					1060					1065					
Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val		
	1070					1075					1080					
Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val		
	1085					1090					1095					
Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val		
	1100					1105					1110					
Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val		
	1115					1120					1125					
Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val		
	1130					1135					1140					
Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val		
	1145					1150					1155					
Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val		
	1160					1165					1170					
Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val		
	1175					1180					1185					
Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val		
	1190					1195					1200					
Pro	Gly	Ala	Gly	Tyr												
	1205															

<210> SEQ ID NO 5
 <211> LENGTH: 728
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 5

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

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Lys	Phe	Lys	Gly	Lys	Ala	Thr	Leu	Thr	Ala	Asp	Lys	Ser	Ser	Ser	Thr	65	70	75	80
Ala	Tyr	Met	Gln	Leu	Ser	Ser	Leu	Thr	Ser	Glu	Asp	Ser	Ala	Val	Tyr	85	90	95	
Tyr	Cys	Ala	Arg	Ser	Thr	Tyr	Tyr	Gly	Gly	Asp	Trp	Tyr	Phe	Asn	Val	100	105	110	
Trp	Gly	Ala	Gly	Thr	Thr	Val	Thr	Val	Ser	Ala	Gly	Gly	Gly	Gly	Ser	115	120	125	
Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gln	Ile	Val	Leu	Ser	Gln	130	135	140	
Ser	Pro	Ala	Ile	Leu	Ser	Ala	Ser	Pro	Gly	Glu	Lys	Val	Thr	Met	Thr	145	150	155	160
Cys	Arg	Ala	Ser	Ser	Ser	Val	Ser	Tyr	Ile	His	Trp	Phe	Gln	Gln	Lys	165	170	175	
Pro	Gly	Ser	Ser	Pro	Lys	Pro	Trp	Ile	Tyr	Ala	Thr	Ser	Asn	Leu	Ala	180	185	190	
Ser	Gly	Val	Pro	Val	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Ser	Tyr	195	200	205	
Ser	Leu	Thr	Ile	Ser	Arg	Val	Glu	Ala	Glu	Asp	Ala	Ala	Thr	Tyr	Tyr	210	215	220	
Cys	Gln	Gln	Trp	Thr	Ser	Asn	Pro	Pro	Thr	Phe	Gly	Gly	Gly	Thr	Lys	225	230	235	240
Leu	Glu	Ile	Lys	Arg	Thr	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	245	250	255	
Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	260	265	270	
Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	275	280	285	
Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	290	295	300	
Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	305	310	315	320
Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	325	330	335	
Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	340	345	350	
Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	355	360	365	
Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	370	375	380	
Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	385	390	395	400
Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	405	410	415	
Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	420	425	430	
Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	435	440	445	
Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	450	455	460	

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Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	465
																470
																475
																480
Phe	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	485
																490
																495
Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	500
																505
																510
Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	515
																520
																525
Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	530
																535
																540
Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	545
																550
																555
																560
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	565
																570
																575
Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	580
																585
																590
Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	595
																600
																605
Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	610
																615
																620
Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	625
																630
																635
																640
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	645
																650
																655
Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	660
																665
																670
Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	675
																680
																685
Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	690
																695
																700
Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	705
																710
																715
																720
Ile	Gly	Val	Pro	Gly	Ile	Gly	Tyr									725

<210> SEQ ID NO 6
 <211> LENGTH: 5
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (4)..(4)
 <223> OTHER INFORMATION: Any amino acid
 <400> SEQUENCE: 6

Val Pro Gly Xaa Gly
 1 5

<210> SEQ ID NO 7
 <211> LENGTH: 2500
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

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polypeptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(2500)
<223> OTHER INFORMATION: This sequence may encompass 1 to 500 "VPGAG"
repeats
<220> FEATURE:
<223> OTHER INFORMATION: See specification as filed for detailed
description of substitutions and preferred embodiments

<400> SEQUENCE: 7

Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val
1 5 10 15
Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro
20 25 30
Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly
35 40 45
Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala
50 55 60
Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly
65 70 75 80
Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val
85 90 95
Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro
100 105 110
Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly
115 120 125
Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala
130 135 140
Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly
145 150 155 160
Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val
165 170 175
Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro
180 185 190
Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly
195 200 205
Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala
210 215 220
Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly
225 230 235 240
Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val
245 250 255
Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro
260 265 270
Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly
275 280 285
Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala
290 295 300
Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly
305 310 315 320
Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val
325 330 335
Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro

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340					345					350				
Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro
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	370					375					380			Ala
Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala
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Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly
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		420					425					430		Pro
Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro
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Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly
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465					470					475				480
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Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val
		500					505					510		Pro
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	530					535					540			Ala
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545					550					555				560
Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly
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Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro
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Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly
	610					615					620			Ala
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		660					665					670		Pro
Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro
	675					680					685			Gly
Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly
	690					695					700			Ala
Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala
705					710					715				720
Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly
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Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val
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Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly
755 760 765

Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala
770 775 780

Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly
785 790 795 800

Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val
805 810 815

Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro
820 825 830

Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly
835 840 845

Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala
850 855 860

Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly
865 870 875 880

Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val
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Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro
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945 950 955 960

Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val
965 970 975

Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro
980 985 990

Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly
995 1000 1005

Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly
1010 1015 1020

Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly
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Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly
1070 1075 1080

Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly
1085 1090 1095

Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly
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Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly
1115 1120 1125

Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly
1130 1135 1140

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Ala Gly 1145	Val Pro Gly	Ala Gly 1150	Val Pro Gly	Ala Gly 1155	Val Pro Gly
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Ala Gly 1190	Val Pro Gly	Ala Gly 1195	Val Pro Gly	Ala Gly 1200	Val Pro Gly
Ala Gly 1205	Val Pro Gly	Ala Gly 1210	Val Pro Gly	Ala Gly 1215	Val Pro Gly
Ala Gly 1220	Val Pro Gly	Ala Gly 1225	Val Pro Gly	Ala Gly 1230	Val Pro Gly
Ala Gly 1235	Val Pro Gly	Ala Gly 1240	Val Pro Gly	Ala Gly 1245	Val Pro Gly
Ala Gly 1250	Val Pro Gly	Ala Gly 1255	Val Pro Gly	Ala Gly 1260	Val Pro Gly
Ala Gly 1265	Val Pro Gly	Ala Gly 1270	Val Pro Gly	Ala Gly 1275	Val Pro Gly
Ala Gly 1280	Val Pro Gly	Ala Gly 1285	Val Pro Gly	Ala Gly 1290	Val Pro Gly
Ala Gly 1295	Val Pro Gly	Ala Gly 1300	Val Pro Gly	Ala Gly 1305	Val Pro Gly
Ala Gly 1310	Val Pro Gly	Ala Gly 1315	Val Pro Gly	Ala Gly 1320	Val Pro Gly
Ala Gly 1325	Val Pro Gly	Ala Gly 1330	Val Pro Gly	Ala Gly 1335	Val Pro Gly
Ala Gly 1340	Val Pro Gly	Ala Gly 1345	Val Pro Gly	Ala Gly 1350	Val Pro Gly
Ala Gly 1355	Val Pro Gly	Ala Gly 1360	Val Pro Gly	Ala Gly 1365	Val Pro Gly
Ala Gly 1370	Val Pro Gly	Ala Gly 1375	Val Pro Gly	Ala Gly 1380	Val Pro Gly
Ala Gly 1385	Val Pro Gly	Ala Gly 1390	Val Pro Gly	Ala Gly 1395	Val Pro Gly
Ala Gly 1400	Val Pro Gly	Ala Gly 1405	Val Pro Gly	Ala Gly 1410	Val Pro Gly
Ala Gly 1415	Val Pro Gly	Ala Gly 1420	Val Pro Gly	Ala Gly 1425	Val Pro Gly
Ala Gly 1430	Val Pro Gly	Ala Gly 1435	Val Pro Gly	Ala Gly 1440	Val Pro Gly
Ala Gly 1445	Val Pro Gly	Ala Gly 1450	Val Pro Gly	Ala Gly 1455	Val Pro Gly
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Ala Gly 1475	Val Pro Gly	Ala Gly 1480	Val Pro Gly	Ala Gly 1485	Val Pro Gly
Ala Gly 1490	Val Pro Gly	Ala Gly 1495	Val Pro Gly	Ala Gly 1500	Val Pro Gly
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Ala Gly	Val Pro Gly	Ala Gly	Val Pro Gly	Ala Gly	Val Pro Gly

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Ala Gly	Val	Pro	Gly	Ala Gly	Val	Pro	Gly	Ala Gly	Val	Pro	Gly
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Ala Gly	Val	Pro	Gly	Ala Gly	Val	Pro	Gly	Ala Gly	Val	Pro	Gly
1565				1570				1575			
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1580				1585				1590			
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1595				1600				1605			
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1610				1615				1620			
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1625				1630				1635			
Ala Gly	Val	Pro	Gly	Ala Gly	Val	Pro	Gly	Ala Gly	Val	Pro	Gly
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Ala Gly	Val	Pro	Gly	Ala Gly	Val	Pro	Gly	Ala Gly	Val	Pro	Gly
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Ala Gly	Val	Pro	Gly	Ala Gly	Val	Pro	Gly	Ala Gly	Val	Pro	Gly
1670				1675				1680			
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1685				1690				1695			
Ala Gly	Val	Pro	Gly	Ala Gly	Val	Pro	Gly	Ala Gly	Val	Pro	Gly
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Ala Gly	Val	Pro	Gly	Ala Gly	Val	Pro	Gly	Ala Gly	Val	Pro	Gly
1760				1765				1770			
Ala Gly	Val	Pro	Gly	Ala Gly	Val	Pro	Gly	Ala Gly	Val	Pro	Gly
1775				1780				1785			
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1790				1795				1800			
Ala Gly	Val	Pro	Gly	Ala Gly	Val	Pro	Gly	Ala Gly	Val	Pro	Gly
1805				1810				1815			
Ala Gly	Val	Pro	Gly	Ala Gly	Val	Pro	Gly	Ala Gly	Val	Pro	Gly
1820				1825				1830			
Ala Gly	Val	Pro	Gly	Ala Gly	Val	Pro	Gly	Ala Gly	Val	Pro	Gly
1835				1840				1845			
Ala Gly	Val	Pro	Gly	Ala Gly	Val	Pro	Gly	Ala Gly	Val	Pro	Gly
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Ala Gly	Val	Pro	Gly	Ala Gly	Val	Pro	Gly	Ala Gly	Val	Pro	Gly
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Ala Gly 1925	Val Pro Gly	Ala Gly 1930	Val Pro Gly	Ala Gly 1935	Val Pro Gly
Ala Gly 1940	Val Pro Gly	Ala Gly 1945	Val Pro Gly	Ala Gly 1950	Val Pro Gly
Ala Gly 1955	Val Pro Gly	Ala Gly 1960	Val Pro Gly	Ala Gly 1965	Val Pro Gly
Ala Gly 1970	Val Pro Gly	Ala Gly 1975	Val Pro Gly	Ala Gly 1980	Val Pro Gly
Ala Gly 1985	Val Pro Gly	Ala Gly 1990	Val Pro Gly	Ala Gly 1995	Val Pro Gly
Ala Gly 2000	Val Pro Gly	Ala Gly 2005	Val Pro Gly	Ala Gly 2010	Val Pro Gly
Ala Gly 2015	Val Pro Gly	Ala Gly 2020	Val Pro Gly	Ala Gly 2025	Val Pro Gly
Ala Gly 2030	Val Pro Gly	Ala Gly 2035	Val Pro Gly	Ala Gly 2040	Val Pro Gly
Ala Gly 2045	Val Pro Gly	Ala Gly 2050	Val Pro Gly	Ala Gly 2055	Val Pro Gly
Ala Gly 2060	Val Pro Gly	Ala Gly 2065	Val Pro Gly	Ala Gly 2070	Val Pro Gly
Ala Gly 2075	Val Pro Gly	Ala Gly 2080	Val Pro Gly	Ala Gly 2085	Val Pro Gly
Ala Gly 2090	Val Pro Gly	Ala Gly 2095	Val Pro Gly	Ala Gly 2100	Val Pro Gly
Ala Gly 2105	Val Pro Gly	Ala Gly 2110	Val Pro Gly	Ala Gly 2115	Val Pro Gly
Ala Gly 2120	Val Pro Gly	Ala Gly 2125	Val Pro Gly	Ala Gly 2130	Val Pro Gly
Ala Gly 2135	Val Pro Gly	Ala Gly 2140	Val Pro Gly	Ala Gly 2145	Val Pro Gly
Ala Gly 2150	Val Pro Gly	Ala Gly 2155	Val Pro Gly	Ala Gly 2160	Val Pro Gly
Ala Gly 2165	Val Pro Gly	Ala Gly 2170	Val Pro Gly	Ala Gly 2175	Val Pro Gly
Ala Gly 2180	Val Pro Gly	Ala Gly 2185	Val Pro Gly	Ala Gly 2190	Val Pro Gly
Ala Gly 2195	Val Pro Gly	Ala Gly 2200	Val Pro Gly	Ala Gly 2205	Val Pro Gly
Ala Gly 2210	Val Pro Gly	Ala Gly 2215	Val Pro Gly	Ala Gly 2220	Val Pro Gly
Ala Gly 2225	Val Pro Gly	Ala Gly 2230	Val Pro Gly	Ala Gly 2235	Val Pro Gly
Ala Gly 2240	Val Pro Gly	Ala Gly 2245	Val Pro Gly	Ala Gly 2250	Val Pro Gly
Ala Gly 2255	Val Pro Gly	Ala Gly 2260	Val Pro Gly	Ala Gly 2265	Val Pro Gly
Ala Gly 2270	Val Pro Gly	Ala Gly 2275	Val Pro Gly	Ala Gly 2280	Val Pro Gly

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Ala Gly	Val Pro Gly	Ala Gly	Val Pro Gly	Ala Gly	Val Pro Gly
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Ala Gly	Val Pro Gly	Ala Gly	Val Pro Gly	Ala Gly	Val Pro Gly
2300		2305		2310	
Ala Gly	Val Pro Gly	Ala Gly	Val Pro Gly	Ala Gly	Val Pro Gly
2315		2320		2325	
Ala Gly	Val Pro Gly	Ala Gly	Val Pro Gly	Ala Gly	Val Pro Gly
2330		2335		2340	
Ala Gly	Val Pro Gly	Ala Gly	Val Pro Gly	Ala Gly	Val Pro Gly
2345		2350		2355	
Ala Gly	Val Pro Gly	Ala Gly	Val Pro Gly	Ala Gly	Val Pro Gly
2360		2365		2370	
Ala Gly	Val Pro Gly	Ala Gly	Val Pro Gly	Ala Gly	Val Pro Gly
2375		2380		2385	
Ala Gly	Val Pro Gly	Ala Gly	Val Pro Gly	Ala Gly	Val Pro Gly
2390		2395		2400	
Ala Gly	Val Pro Gly	Ala Gly	Val Pro Gly	Ala Gly	Val Pro Gly
2405		2410		2415	
Ala Gly	Val Pro Gly	Ala Gly	Val Pro Gly	Ala Gly	Val Pro Gly
2420		2425		2430	
Ala Gly	Val Pro Gly	Ala Gly	Val Pro Gly	Ala Gly	Val Pro Gly
2435		2440		2445	
Ala Gly	Val Pro Gly	Ala Gly	Val Pro Gly	Ala Gly	Val Pro Gly
2450		2455		2460	
Ala Gly	Val Pro Gly	Ala Gly	Val Pro Gly	Ala Gly	Val Pro Gly
2465		2470		2475	
Ala Gly	Val Pro Gly	Ala Gly	Val Pro Gly	Ala Gly	Val Pro Gly
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Ala Gly	Val Pro Gly	Ala Gly			
2495		2500			

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 <220> FEATURE:
 <223> OTHER INFORMATION: See specification as filed for detailed description of substitutions and preferred embodiments
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Pro Gly	Ala Gly	Val Pro Gly	Ala Gly	Val Pro Gly	Ala Gly	Val Pro
	20		25		30	
Gly	Ala Gly	Val Pro Gly	Ala Gly	Val Pro Gly	Ala Gly	Val Pro Gly

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35	40	45
Ala Gly Val Pro Gly	Ala Gly Val Pro Gly	Ala Gly Val Pro Gly Ala
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Gly Val Pro Gly Ala	Gly Val Pro Gly Ala	Gly Val Pro Gly Ala Gly
65	70	75 80
Val Pro Gly Ala Gly	Val Pro Gly Ala Gly	Val Pro Gly Ala Gly Val
85	90	95
Pro Gly Ala Gly Val	Pro Gly Ala Gly Val	Pro Gly Ala Gly Val Pro
100	105	110
Gly Ala Gly Val Pro	Gly Ala Gly Val Pro	Gly Ala Gly Val Pro Gly
115	120	125
Ala Gly Val Pro Gly	Ala Gly Val Pro Gly	Ala Gly Val Pro Gly Ala
130	135	140
Gly Val Pro Gly Ala	Gly Val Pro Gly Ala	Gly Val Pro Gly Ala Gly
145	150	155 160
Val Pro Gly Ala Gly	Val Pro Gly Ala Gly	Val Pro Gly Ala Gly Val
165	170	175
Pro Gly Ala Gly Val	Pro Gly Ala Gly Val	Pro Gly Ala Gly Val Pro
180	185	190
Gly Ala Gly Val Pro	Gly Ala Gly Val Pro	Gly Ala Gly Val Pro Gly
195	200	205
Ala Gly Val Pro Gly	Ala Gly Val Pro Gly	Ala Gly Val Pro Gly Ala
210	215	220
Gly Val Pro Gly Ala	Gly Val Pro Gly Ala	Gly Val Pro Gly Ala Gly
225	230	235 240
Val Pro Gly Ala Gly	Val Pro Gly Ala Gly	Val Pro Gly Ala Gly Val
245	250	255
Pro Gly Ala Gly Val	Pro Gly Ala Gly Val	Pro Gly Ala Gly Val Pro
260	265	270
Gly Ala Gly Val Pro	Gly Ala Gly Val Pro	Gly Ala Gly Val Pro Gly
275	280	285
Ala Gly Val Pro Gly	Ala Gly Val Pro Gly	Ala Gly Val Pro Gly Ala
290	295	300
Gly Val Pro Gly Ala	Gly Val Pro Gly Ala	Gly Val Pro Gly Ala Gly
305	310	315 320
Val Pro Gly Ala Gly	Val Pro Gly Ala Gly	Val Pro Gly Ala Gly Val
325	330	335
Pro Gly Ala Gly Val	Pro Gly Ala Gly Val	Pro Gly Ala Gly Val Pro
340	345	350
Gly Ala Gly Val Pro	Gly Ala Gly Val Pro	Gly Ala Gly Val Pro Gly
355	360	365
Ala Gly Val Pro Gly	Ala Gly Val Pro Gly	Ala Gly Val Pro Gly Ala
370	375	380
Gly Val Pro Gly Ala	Gly Val Pro Gly Ala	Gly Val Pro Gly Ala Gly
385	390	395 400
Val Pro Gly Ala Gly	Val Pro Gly Ala Gly	Val Pro Gly Ala Gly Val
405	410	415
Pro Gly Ala Gly Val	Pro Gly Ala Gly Val	Pro Gly Ala Gly Val Pro
420	425	430
Gly Ala Gly Val Pro	Gly Ala Gly Val Pro	Gly Ala Gly Val Pro Gly
435	440	445

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Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala
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Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly
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Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val
485 490 495

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500 505 510

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565 570 575

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580 585 590

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595 600 605

Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala
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Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val
645 650 655

Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro
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675 680 685

Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala
690 695 700

Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly
705 710 715 720

Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val
725 730 735

Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro
740 745 750

Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly
755 760 765

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770 775 780

Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly
785 790 795 800

Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val
805 810 815

Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro
820 825 830

Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly
835 840 845

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Ala Gly Val Pro Gly	Ala Gly Val Pro Gly	Ala Gly Val Pro Gly	Ala Gly Val Pro Gly
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Gly Val Pro Gly Ala	Gly Val Pro Gly Ala	Gly Val Pro Gly Ala	Gly
865	870	875	880
Val Pro Gly Ala Gly	Val Pro Gly Ala Gly	Val Pro Gly Ala Gly	Val
885	890	895	
Pro Gly Ala Gly Val	Pro Gly Ala Gly Val	Pro Gly Ala Gly Val	Pro
900	905	910	
Gly Ala Gly Val Pro	Gly Ala Gly Val Pro	Gly Ala Gly Val Pro	Gly
915	920	925	
Ala Gly Val Pro Gly	Ala Gly Val Pro Gly	Ala Gly Val Pro Gly	Ala
930	935	940	
Gly Val Pro Gly Ala	Gly Val Pro Gly Ala	Gly Val Pro Gly Ala	Gly
945	950	955	960
Val Pro Gly Ala Gly	Val Pro Gly Ala Gly	Val Pro Gly Ala Gly	Val
965	970	975	
Pro Gly Ala Gly Val	Pro Gly Ala Gly Val	Pro Gly Ala Gly Val	Pro
980	985	990	
Gly Ala Gly Val Pro	Gly Ala Gly Val Pro	Gly Ala Gly Val Pro	Gly
995	1000	1005	
Ala Gly Val Pro Gly	Ala Gly Val Pro Gly	Ala Gly Val Pro Gly	
1010	1015	1020	
Ala Gly Val Pro Gly	Ala Gly Val Pro Gly	Ala Gly Val Pro Gly	
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Ala Gly Val Pro Gly	Ala Gly Val Pro Gly	Ala Gly Val Pro Gly	
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Ala Gly Val Pro Gly	Ala Gly Val Pro Gly	Ala Gly Val Pro Gly	
1055	1060	1065	
Ala Gly Val Pro Gly	Ala Gly Val Pro Gly	Ala Gly Val Pro Gly	
1070	1075	1080	
Ala Gly Val Pro Gly	Ala Gly Val Pro Gly	Ala Gly Val Pro Gly	
1085	1090	1095	
Ala Gly Val Pro Gly	Ala Gly Val Pro Gly	Ala Gly Val Pro Gly	
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Ala Gly Val Pro Gly	Ala Gly Val Pro Gly	Ala Gly Val Pro Gly	
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1160	1165	1170	
Ala Gly Val Pro Gly	Ala Gly Val Pro Gly	Ala Gly Val Pro Gly	
1175	1180	1185	
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Ala Gly Val Pro Gly	Ala Gly Val Pro Gly	Ala Gly Val Pro Gly	
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Ala Gly Val Pro Gly	Ala Gly Val Pro Gly	Ala Gly Val Pro Gly	

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Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly		
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1310	1315	1320
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1325	1330	1335
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1340	1345	1350
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1355	1360	1365
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1370	1375	1380
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1385	1390	1395
Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly		
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Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly		
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Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly		
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Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly		
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Ala Gly 1655	Val Pro Gly	Ala Gly 1660	Val Pro Gly	Ala Gly 1665	Val Pro Gly
Ala Gly 1670	Val Pro Gly	Ala Gly 1675	Val Pro Gly	Ala Gly 1680	Val Pro Gly
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Ala Gly 1700	Val Pro Gly	Ala Gly 1705	Val Pro Gly	Ala Gly 1710	Val Pro Gly
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Ala Gly 1730	Val Pro Gly	Ala Gly 1735	Val Pro Gly	Ala Gly 1740	Val Pro Gly
Ala Gly 1745	Val Pro Gly	Ala Gly 1750	Val Pro Gly	Ala Gly 1755	Val Pro Gly
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Ala Gly 1775	Val Pro Gly	Ala Gly 1780	Val Pro Gly	Ala Gly 1785	Val Pro Gly
Ala Gly 1790	Val Pro Gly	Ala Gly 1795	Val Pro Gly	Ala Gly 1800	Val Pro Gly
Ala Gly 1805	Val Pro Gly	Ala Gly 1810	Val Pro Gly	Ala Gly 1815	Val Pro Gly
Ala Gly 1820	Val Pro Gly	Ala Gly 1825	Val Pro Gly	Ala Gly 1830	Val Pro Gly
Ala Gly 1835	Val Pro Gly	Ala Gly 1840	Val Pro Gly	Ala Gly 1845	Val Pro Gly
Ala Gly 1850	Val Pro Gly	Ala Gly 1855	Val Pro Gly	Ala Gly 1860	Val Pro Gly
Ala Gly 1865	Val Pro Gly	Ala Gly 1870	Val Pro Gly	Ala Gly 1875	Val Pro Gly
Ala Gly 1880	Val Pro Gly	Ala Gly 1885	Val Pro Gly	Ala Gly 1890	Val Pro Gly
Ala Gly 1895	Val Pro Gly	Ala Gly 1900	Val Pro Gly	Ala Gly 1905	Val Pro Gly
Ala Gly 1910	Val Pro Gly	Ala Gly 1915	Val Pro Gly	Ala Gly 1920	Val Pro Gly
Ala Gly 1925	Val Pro Gly	Ala Gly 1930	Val Pro Gly	Ala Gly 1935	Val Pro Gly
Ala Gly 1940	Val Pro Gly	Ala Gly 1945	Val Pro Gly	Ala Gly 1950	Val Pro Gly
Ala Gly 1955	Val Pro Gly	Ala Gly 1960	Val Pro Gly	Ala Gly 1965	Val Pro Gly
Ala Gly 1970	Val Pro Gly	Ala Gly 1975	Val Pro Gly	Ala Gly 1980	Val Pro Gly
Ala Gly 1985	Val Pro Gly	Ala Gly 1990	Val Pro Gly	Ala Gly 1995	Val Pro Gly

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Ala Gly 2000	Val	Pro	Gly	Ala Gly 2005	Val	Pro	Gly	Ala Gly 2010	Val	Pro	Gly
Ala Gly 2015	Val	Pro	Gly	Ala Gly 2020	Val	Pro	Gly	Ala Gly 2025	Val	Pro	Gly
Ala Gly 2030	Val	Pro	Gly	Ala Gly 2035	Val	Pro	Gly	Ala Gly 2040	Val	Pro	Gly
Ala Gly 2045	Val	Pro	Gly	Ala Gly 2050	Val	Pro	Gly	Ala Gly 2055	Val	Pro	Gly
Ala Gly 2060	Val	Pro	Gly	Ala Gly 2065	Val	Pro	Gly	Ala Gly 2070	Val	Pro	Gly
Ala Gly 2075	Val	Pro	Gly	Ala Gly 2080	Val	Pro	Gly	Ala Gly 2085	Val	Pro	Gly
Ala Gly 2090	Val	Pro	Gly	Ala Gly 2095	Val	Pro	Gly	Ala Gly 2100	Val	Pro	Gly
Ala Gly 2105	Val	Pro	Gly	Ala Gly 2110	Val	Pro	Gly	Ala Gly 2115	Val	Pro	Gly
Ala Gly 2120	Val	Pro	Gly	Ala Gly 2125	Val	Pro	Gly	Ala Gly 2130	Val	Pro	Gly
Ala Gly 2135	Val	Pro	Gly	Ala Gly 2140	Val	Pro	Gly	Ala Gly 2145	Val	Pro	Gly
Ala Gly 2150	Val	Pro	Gly	Ala Gly 2155	Val	Pro	Gly	Ala Gly 2160	Val	Pro	Gly
Ala Gly 2165	Val	Pro	Gly	Ala Gly 2170	Val	Pro	Gly	Ala Gly 2175	Val	Pro	Gly
Ala Gly 2180	Val	Pro	Gly	Ala Gly 2185	Val	Pro	Gly	Ala Gly 2190	Val	Pro	Gly
Ala Gly 2195	Val	Pro	Gly	Ala Gly 2200	Val	Pro	Gly	Ala Gly 2205	Val	Pro	Gly
Ala Gly 2210	Val	Pro	Gly	Ala Gly 2215	Val	Pro	Gly	Ala Gly 2220	Val	Pro	Gly
Ala Gly 2225	Val	Pro	Gly	Ala Gly 2230	Val	Pro	Gly	Ala Gly 2235	Val	Pro	Gly
Ala Gly 2240	Val	Pro	Gly	Ala Gly 2245	Val	Pro	Gly	Ala Gly 2250	Val	Pro	Gly
Ala Gly 2255	Val	Pro	Gly	Ala Gly 2260	Val	Pro	Gly	Ala Gly 2265	Val	Pro	Gly
Ala Gly 2270	Val	Pro	Gly	Ala Gly 2275	Val	Pro	Gly	Ala Gly 2280	Val	Pro	Gly
Ala Gly 2285	Val	Pro	Gly	Ala Gly 2290	Val	Pro	Gly	Ala Gly 2295	Val	Pro	Gly
Ala Gly 2300	Val	Pro	Gly	Ala Gly 2305	Val	Pro	Gly	Ala Gly 2310	Val	Pro	Gly
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Ala Gly 2345	Val	Pro	Gly	Ala Gly 2350	Val	Pro	Gly	Ala Gly 2355	Val	Pro	Gly
Ala Gly 2360	Val	Pro	Gly	Ala Gly 2365	Val	Pro	Gly	Ala Gly 2370	Val	Pro	Gly
Ala Gly	Val	Pro	Gly	Ala Gly	Val	Pro	Gly	Ala Gly	Val	Pro	Gly

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2390	2395	2400
Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly		
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Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly		
2420	2425	2430
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2435	2440	2445
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Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ile Gly Val Pro Gly		
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Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly		
2510	2515	2520
Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly		
2525	2530	2535
Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly		
2540	2545	2550
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Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly		
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Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly		
2585	2590	2595
Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly		
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Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly		
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Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly		
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Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly		
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Ile Gly 2810	Val Pro Gly	Ile Gly 2815	Val Pro Gly	Ile Gly 2820	Val Pro Gly
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Ile Gly 2840	Val Pro Gly	Ile Gly 2845	Val Pro Gly	Ile Gly 2850	Val Pro Gly
Ile Gly 2855	Val Pro Gly	Ile Gly 2860	Val Pro Gly	Ile Gly 2865	Val Pro Gly
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Ile Gly 2900	Val Pro Gly	Ile Gly 2905	Val Pro Gly	Ile Gly 2910	Val Pro Gly
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Ile Gly 3095	Val Pro Gly	Ile Gly 3100	Val Pro Gly	Ile Gly 3105	Val Pro Gly
Ile Gly 3110	Val Pro Gly	Ile Gly 3115	Val Pro Gly	Ile Gly 3120	Val Pro Gly
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Ile Gly 3425	Val Pro Gly	Ile Gly 3430	Val Pro Gly	Ile Gly 3435	Val Pro Gly
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Ile Gly 3470	Val Pro Gly	Ile Gly 3475	Val Pro Gly	Ile Gly 3480	Val Pro Gly
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Ile Gly	Val Pro Gly	Ile Gly	Val Pro Gly	Ile Gly	Val Pro Gly

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Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly
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Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly
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Ile Gly 3920	Val Pro Gly	Ile Gly 3925	Val Pro Gly	Ile Gly 3930	Val Pro Gly
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Ile Gly 3950	Val Pro Gly	Ile Gly 3955	Val Pro Gly	Ile Gly 3960	Val Pro Gly
Ile Gly 3965	Val Pro Gly	Ile Gly 3970	Val Pro Gly	Ile Gly 3975	Val Pro Gly
Ile Gly 3980	Val Pro Gly	Ile Gly 3985	Val Pro Gly	Ile Gly 3990	Val Pro Gly
Ile Gly 3995	Val Pro Gly	Ile Gly 4000	Val Pro Gly	Ile Gly 4005	Val Pro Gly
Ile Gly 4010	Val Pro Gly	Ile Gly 4015	Val Pro Gly	Ile Gly 4020	Val Pro Gly
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Ile Gly 4055	Val Pro Gly	Ile Gly 4060	Val Pro Gly	Ile Gly 4065	Val Pro Gly
Ile Gly 4070	Val Pro Gly	Ile Gly 4075	Val Pro Gly	Ile Gly 4080	Val Pro Gly
Ile Gly 4085	Val Pro Gly	Ile Gly 4090	Val Pro Gly	Ile Gly 4095	Val Pro Gly
Ile Gly 4100	Val Pro Gly	Ile Gly 4105	Val Pro Gly	Ile Gly 4110	Val Pro Gly
Ile Gly 4115	Val Pro Gly	Ile Gly 4120	Val Pro Gly	Ile Gly 4125	Val Pro Gly
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Ile Gly 4235	Val Pro Gly	Ile Gly 4240	Val Pro Gly	Ile Gly 4245	Val Pro Gly
Ile Gly 4250	Val Pro Gly	Ile Gly 4255	Val Pro Gly	Ile Gly 4260	Val Pro Gly
Ile Gly 4265	Val Pro Gly	Ile Gly 4270	Val Pro Gly	Ile Gly 4275	Val Pro Gly

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Ile Gly 4325	Val Pro Gly	Ile Gly 4330	Val Pro Gly	Ile Gly 4335	Val Pro Gly
Ile Gly 4340	Val Pro Gly	Ile Gly 4345	Val Pro Gly	Ile Gly 4350	Val Pro Gly
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Ile Gly 4370	Val Pro Gly	Ile Gly 4375	Val Pro Gly	Ile Gly 4380	Val Pro Gly
Ile Gly 4385	Val Pro Gly	Ile Gly 4390	Val Pro Gly	Ile Gly 4395	Val Pro Gly
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Ile Gly 4445	Val Pro Gly	Ile Gly 4450	Val Pro Gly	Ile Gly 4455	Val Pro Gly
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Ile Gly 4625	Val Pro Gly	Ile Gly 4630	Val Pro Gly	Ile Gly 4635	Val Pro Gly
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Ile Gly	Val Pro Gly	Ile Gly	Val Pro Gly	Ile Gly	Val Pro Gly

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4685	4690	4695
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4730	4735	4740
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4745	4750	4755
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4760	4765	4770
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4850	4855	4860
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4925	4930	4935
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4940	4945	4950
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4955	4960	4965
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Ile Gly		
5000		

<210> SEQ ID NO 9

<211> LENGTH: 5000

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

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<223> OTHER INFORMATION: This region may encompass 1 to 500 "VPGSG" repeats
<220> FEATURE:
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<222> LOCATION: (2501)..(5000)
<223> OTHER INFORMATION: This region may encompass 1 to 500 "VPGIG" repeats
<220> FEATURE:
<223> OTHER INFORMATION: See specification as filed for detailed description of substitutions and preferred embodiments

<400> SEQUENCE: 9

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Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly
35 40 45
Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser
50 55 60
Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly
65 70 75 80
Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val
85 90 95
Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro
100 105 110
Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly
115 120 125
Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser
130 135 140
Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly
145 150 155 160
Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val
165 170 175
Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro
180 185 190
Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly
195 200 205
Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser
210 215 220
Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly
225 230 235 240
Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val
245 250 255
Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro
260 265 270
Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly
275 280 285
Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser
290 295 300

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Gly Val Pro Gly Ser	Gly Val Pro Gly Ser	Gly Val Pro Gly Ser	Gly Val Pro Gly Ser	Gly Val Pro Gly Ser
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	325	330	335	
Pro Gly Ser Gly Val	Pro Gly Ser Gly Val	Pro Gly Ser Gly Val	Pro Gly Ser Gly Val	Pro Gly Ser Gly Val
	340	345	350	
Gly Ser Gly Val Pro	Gly Ser Gly Val Pro	Gly Ser Gly Val Pro	Gly Ser Gly Val Pro	Gly Ser Gly Val Pro
	355	360	365	
Ser Gly Val Pro Gly	Ser Gly Val Pro Gly	Ser Gly Val Pro Gly	Ser Gly Val Pro Gly	Ser Gly Val Pro Gly
	370	375	380	
Gly Val Pro Gly Ser	Gly Val Pro Gly Ser	Gly Val Pro Gly Ser	Gly Val Pro Gly Ser	Gly Val Pro Gly Ser
	385	390	395	400
Val Pro Gly Ser Gly	Val Pro Gly Ser Gly	Val Pro Gly Ser Gly	Val Pro Gly Ser Gly	Val Pro Gly Ser Gly
	405	410	415	
Pro Gly Ser Gly Val	Pro Gly Ser Gly Val	Pro Gly Ser Gly Val	Pro Gly Ser Gly Val	Pro Gly Ser Gly Val
	420	425	430	
Gly Ser Gly Val Pro	Gly Ser Gly Val Pro	Gly Ser Gly Val Pro	Gly Ser Gly Val Pro	Gly Ser Gly Val Pro
	435	440	445	
Ser Gly Val Pro Gly	Ser Gly Val Pro Gly	Ser Gly Val Pro Gly	Ser Gly Val Pro Gly	Ser Gly Val Pro Gly
	450	455	460	
Gly Val Pro Gly Ser	Gly Val Pro Gly Ser	Gly Val Pro Gly Ser	Gly Val Pro Gly Ser	Gly Val Pro Gly Ser
	465	470	475	480
Val Pro Gly Ser Gly	Val Pro Gly Ser Gly	Val Pro Gly Ser Gly	Val Pro Gly Ser Gly	Val Pro Gly Ser Gly
	485	490	495	
Pro Gly Ser Gly Val	Pro Gly Ser Gly Val	Pro Gly Ser Gly Val	Pro Gly Ser Gly Val	Pro Gly Ser Gly Val
	500	505	510	
Gly Ser Gly Val Pro	Gly Ser Gly Val Pro	Gly Ser Gly Val Pro	Gly Ser Gly Val Pro	Gly Ser Gly Val Pro
	515	520	525	
Ser Gly Val Pro Gly	Ser Gly Val Pro Gly	Ser Gly Val Pro Gly	Ser Gly Val Pro Gly	Ser Gly Val Pro Gly
	530	535	540	
Gly Val Pro Gly Ser	Gly Val Pro Gly Ser	Gly Val Pro Gly Ser	Gly Val Pro Gly Ser	Gly Val Pro Gly Ser
	545	550	555	560
Val Pro Gly Ser Gly	Val Pro Gly Ser Gly	Val Pro Gly Ser Gly	Val Pro Gly Ser Gly	Val Pro Gly Ser Gly
	565	570	575	
Pro Gly Ser Gly Val	Pro Gly Ser Gly Val	Pro Gly Ser Gly Val	Pro Gly Ser Gly Val	Pro Gly Ser Gly Val
	580	585	590	
Gly Ser Gly Val Pro	Gly Ser Gly Val Pro	Gly Ser Gly Val Pro	Gly Ser Gly Val Pro	Gly Ser Gly Val Pro
	595	600	605	
Ser Gly Val Pro Gly	Ser Gly Val Pro Gly	Ser Gly Val Pro Gly	Ser Gly Val Pro Gly	Ser Gly Val Pro Gly
	610	615	620	
Gly Val Pro Gly Ser	Gly Val Pro Gly Ser	Gly Val Pro Gly Ser	Gly Val Pro Gly Ser	Gly Val Pro Gly Ser
	625	630	635	640
Val Pro Gly Ser Gly	Val Pro Gly Ser Gly	Val Pro Gly Ser Gly	Val Pro Gly Ser Gly	Val Pro Gly Ser Gly
	645	650	655	
Pro Gly Ser Gly Val	Pro Gly Ser Gly Val	Pro Gly Ser Gly Val	Pro Gly Ser Gly Val	Pro Gly Ser Gly Val
	660	665	670	
Gly Ser Gly Val Pro	Gly Ser Gly Val Pro	Gly Ser Gly Val Pro	Gly Ser Gly Val Pro	Gly Ser Gly Val Pro
	675	680	685	
Ser Gly Val Pro Gly	Ser Gly Val Pro Gly	Ser Gly Val Pro Gly	Ser Gly Val Pro Gly	Ser Gly Val Pro Gly
	690	695	700	
Gly Val Pro Gly Ser	Gly Val Pro Gly Ser	Gly Val Pro Gly Ser	Gly Val Pro Gly Ser	Gly Val Pro Gly Ser

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705					710					715					720
Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val
				725					730					735	
Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro
			740					745					750		
Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly
	755					760					765				
Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser
	770					775					780				
Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly
785				790				795					800		
Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val
			805					810					815		
Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro
		820					825					830			
Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly
	835					840					845				
Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser
	850					855					860				
Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly
865				870				875					880		
Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val
			885					890					895		
Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro
		900					905					910			
Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly
	915					920					925				
Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser
	930					935					940				
Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly
945				950				955					960		
Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val
			965					970					975		
Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro
		980					985					990			
Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly
	995					1000					1005				
Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	
	1010					1015					1020				
Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	
	1025					1030					1035				
Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	
	1040					1045					1050				
Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	
	1055					1060					1065				
Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	
	1070					1075					1080				
Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	
	1085					1090					1095				
Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	Ser	Gly	Val	Pro	Gly	
	1100					1105					1110				

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Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly
1115		1120		1125	
Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly
1130		1135		1140	
Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly
1145		1150		1155	
Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly
1160		1165		1170	
Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly
1175		1180		1185	
Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly
1190		1195		1200	
Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly
1205		1210		1215	
Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly
1220		1225		1230	
Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly
1235		1240		1245	
Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly
1250		1255		1260	
Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly
1265		1270		1275	
Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly
1280		1285		1290	
Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly
1295		1300		1305	
Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly
1310		1315		1320	
Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly
1325		1330		1335	
Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly
1340		1345		1350	
Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly
1355		1360		1365	
Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly
1370		1375		1380	
Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly
1385		1390		1395	
Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly
1400		1405		1410	
Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly
1415		1420		1425	
Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly
1430		1435		1440	
Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly
1445		1450		1455	
Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly
1460		1465		1470	
Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly
1475		1480		1485	

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Ser Gly 1490	Val Pro Gly	Ser Gly 1495	Val Pro Gly	Ser Gly 1500	Val Pro Gly
Ser Gly 1505	Val Pro Gly	Ser Gly 1510	Val Pro Gly	Ser Gly 1515	Val Pro Gly
Ser Gly 1520	Val Pro Gly	Ser Gly 1525	Val Pro Gly	Ser Gly 1530	Val Pro Gly
Ser Gly 1535	Val Pro Gly	Ser Gly 1540	Val Pro Gly	Ser Gly 1545	Val Pro Gly
Ser Gly 1550	Val Pro Gly	Ser Gly 1555	Val Pro Gly	Ser Gly 1560	Val Pro Gly
Ser Gly 1565	Val Pro Gly	Ser Gly 1570	Val Pro Gly	Ser Gly 1575	Val Pro Gly
Ser Gly 1580	Val Pro Gly	Ser Gly 1585	Val Pro Gly	Ser Gly 1590	Val Pro Gly
Ser Gly 1595	Val Pro Gly	Ser Gly 1600	Val Pro Gly	Ser Gly 1605	Val Pro Gly
Ser Gly 1610	Val Pro Gly	Ser Gly 1615	Val Pro Gly	Ser Gly 1620	Val Pro Gly
Ser Gly 1625	Val Pro Gly	Ser Gly 1630	Val Pro Gly	Ser Gly 1635	Val Pro Gly
Ser Gly 1640	Val Pro Gly	Ser Gly 1645	Val Pro Gly	Ser Gly 1650	Val Pro Gly
Ser Gly 1655	Val Pro Gly	Ser Gly 1660	Val Pro Gly	Ser Gly 1665	Val Pro Gly
Ser Gly 1670	Val Pro Gly	Ser Gly 1675	Val Pro Gly	Ser Gly 1680	Val Pro Gly
Ser Gly 1685	Val Pro Gly	Ser Gly 1690	Val Pro Gly	Ser Gly 1695	Val Pro Gly
Ser Gly 1700	Val Pro Gly	Ser Gly 1705	Val Pro Gly	Ser Gly 1710	Val Pro Gly
Ser Gly 1715	Val Pro Gly	Ser Gly 1720	Val Pro Gly	Ser Gly 1725	Val Pro Gly
Ser Gly 1730	Val Pro Gly	Ser Gly 1735	Val Pro Gly	Ser Gly 1740	Val Pro Gly
Ser Gly 1745	Val Pro Gly	Ser Gly 1750	Val Pro Gly	Ser Gly 1755	Val Pro Gly
Ser Gly 1760	Val Pro Gly	Ser Gly 1765	Val Pro Gly	Ser Gly 1770	Val Pro Gly
Ser Gly 1775	Val Pro Gly	Ser Gly 1780	Val Pro Gly	Ser Gly 1785	Val Pro Gly
Ser Gly 1790	Val Pro Gly	Ser Gly 1795	Val Pro Gly	Ser Gly 1800	Val Pro Gly
Ser Gly 1805	Val Pro Gly	Ser Gly 1810	Val Pro Gly	Ser Gly 1815	Val Pro Gly
Ser Gly 1820	Val Pro Gly	Ser Gly 1825	Val Pro Gly	Ser Gly 1830	Val Pro Gly
Ser Gly 1835	Val Pro Gly	Ser Gly 1840	Val Pro Gly	Ser Gly 1845	Val Pro Gly
Ser Gly 1850	Val Pro Gly	Ser Gly 1855	Val Pro Gly	Ser Gly 1860	Val Pro Gly
Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly	Ser Gly	Val Pro Gly

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1865		1870		1875
Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly				
1880		1885		1890
Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly				
1895		1900		1905
Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly				
1910		1915		1920
Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly				
1925		1930		1935
Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly				
1940		1945		1950
Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly				
1955		1960		1965
Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly				
1970		1975		1980
Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly				
1985		1990		1995
Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly				
2000		2005		2010
Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly				
2015		2020		2025
Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly				
2030		2035		2040
Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly				
2045		2050		2055
Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly				
2060		2065		2070
Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly				
2075		2080		2085
Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly				
2090		2095		2100
Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly				
2105		2110		2115
Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly				
2120		2125		2130
Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly				
2135		2140		2145
Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly				
2150		2155		2160
Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly				
2165		2170		2175
Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly				
2180		2185		2190
Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly				
2195		2200		2205
Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly				
2210		2215		2220
Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly				
2225		2230		2235
Ser Gly Val Pro Gly Ser Gly Val Pro Gly Ser Gly Val Pro Gly				
2240		2245		2250

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Ser Gly 2255	Val Pro Gly Ser Gly 2260	Val Pro Gly Ser Gly 2265	Val Pro Gly
Ser Gly 2270	Val Pro Gly Ser Gly 2275	Ser Gly 2280	Val Pro Gly
Ser Gly 2285	Val Pro Gly Ser Gly 2290	Ser Gly 2295	Val Pro Gly
Ser Gly 2300	Val Pro Gly Ser Gly 2305	Ser Gly 2310	Val Pro Gly
Ser Gly 2315	Val Pro Gly Ser Gly 2320	Ser Gly 2325	Val Pro Gly
Ser Gly 2330	Val Pro Gly Ser Gly 2335	Ser Gly 2340	Val Pro Gly
Ser Gly 2345	Val Pro Gly Ser Gly 2350	Ser Gly 2355	Val Pro Gly
Ser Gly 2360	Val Pro Gly Ser Gly 2365	Ser Gly 2370	Val Pro Gly
Ser Gly 2375	Val Pro Gly Ser Gly 2380	Ser Gly 2385	Val Pro Gly
Ser Gly 2390	Val Pro Gly Ser Gly 2395	Ser Gly 2400	Val Pro Gly
Ser Gly 2405	Val Pro Gly Ser Gly 2410	Ser Gly 2415	Val Pro Gly
Ser Gly 2420	Val Pro Gly Ser Gly 2425	Ser Gly 2430	Val Pro Gly
Ser Gly 2435	Val Pro Gly Ser Gly 2440	Ser Gly 2445	Val Pro Gly
Ser Gly 2450	Val Pro Gly Ser Gly 2455	Ser Gly 2460	Val Pro Gly
Ser Gly 2465	Val Pro Gly Ser Gly 2470	Ser Gly 2475	Val Pro Gly
Ser Gly 2480	Val Pro Gly Ser Gly 2485	Ser Gly 2490	Val Pro Gly
Ser Gly 2495	Val Pro Gly Ser Gly 2500	Ser Gly 2505	Val Pro Gly
Ile Gly 2510	Val Pro Gly Ile Gly 2515	Ile Gly 2520	Val Pro Gly
Ile Gly 2525	Val Pro Gly Ile Gly 2530	Ile Gly 2535	Val Pro Gly
Ile Gly 2540	Val Pro Gly Ile Gly 2545	Ile Gly 2550	Val Pro Gly
Ile Gly 2555	Val Pro Gly Ile Gly 2560	Ile Gly 2565	Val Pro Gly
Ile Gly 2570	Val Pro Gly Ile Gly 2575	Ile Gly 2580	Val Pro Gly
Ile Gly 2585	Val Pro Gly Ile Gly 2590	Ile Gly 2595	Val Pro Gly
Ile Gly 2600	Val Pro Gly Ile Gly 2605	Ile Gly 2610	Val Pro Gly
Ile Gly 2615	Val Pro Gly Ile Gly 2620	Ile Gly 2625	Val Pro Gly

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Ile Gly 2630	Val Pro Gly	Ile Gly 2635	Val Pro Gly	Ile Gly 2640	Val Pro Gly
Ile Gly 2645	Val Pro Gly	Ile Gly 2650	Val Pro Gly	Ile Gly 2655	Val Pro Gly
Ile Gly 2660	Val Pro Gly	Ile Gly 2665	Val Pro Gly	Ile Gly 2670	Val Pro Gly
Ile Gly 2675	Val Pro Gly	Ile Gly 2680	Val Pro Gly	Ile Gly 2685	Val Pro Gly
Ile Gly 2690	Val Pro Gly	Ile Gly 2695	Val Pro Gly	Ile Gly 2700	Val Pro Gly
Ile Gly 2705	Val Pro Gly	Ile Gly 2710	Val Pro Gly	Ile Gly 2715	Val Pro Gly
Ile Gly 2720	Val Pro Gly	Ile Gly 2725	Val Pro Gly	Ile Gly 2730	Val Pro Gly
Ile Gly 2735	Val Pro Gly	Ile Gly 2740	Val Pro Gly	Ile Gly 2745	Val Pro Gly
Ile Gly 2750	Val Pro Gly	Ile Gly 2755	Val Pro Gly	Ile Gly 2760	Val Pro Gly
Ile Gly 2765	Val Pro Gly	Ile Gly 2770	Val Pro Gly	Ile Gly 2775	Val Pro Gly
Ile Gly 2780	Val Pro Gly	Ile Gly 2785	Val Pro Gly	Ile Gly 2790	Val Pro Gly
Ile Gly 2795	Val Pro Gly	Ile Gly 2800	Val Pro Gly	Ile Gly 2805	Val Pro Gly
Ile Gly 2810	Val Pro Gly	Ile Gly 2815	Val Pro Gly	Ile Gly 2820	Val Pro Gly
Ile Gly 2825	Val Pro Gly	Ile Gly 2830	Val Pro Gly	Ile Gly 2835	Val Pro Gly
Ile Gly 2840	Val Pro Gly	Ile Gly 2845	Val Pro Gly	Ile Gly 2850	Val Pro Gly
Ile Gly 2855	Val Pro Gly	Ile Gly 2860	Val Pro Gly	Ile Gly 2865	Val Pro Gly
Ile Gly 2870	Val Pro Gly	Ile Gly 2875	Val Pro Gly	Ile Gly 2880	Val Pro Gly
Ile Gly 2885	Val Pro Gly	Ile Gly 2890	Val Pro Gly	Ile Gly 2895	Val Pro Gly
Ile Gly 2900	Val Pro Gly	Ile Gly 2905	Val Pro Gly	Ile Gly 2910	Val Pro Gly
Ile Gly 2915	Val Pro Gly	Ile Gly 2920	Val Pro Gly	Ile Gly 2925	Val Pro Gly
Ile Gly 2930	Val Pro Gly	Ile Gly 2935	Val Pro Gly	Ile Gly 2940	Val Pro Gly
Ile Gly 2945	Val Pro Gly	Ile Gly 2950	Val Pro Gly	Ile Gly 2955	Val Pro Gly
Ile Gly 2960	Val Pro Gly	Ile Gly 2965	Val Pro Gly	Ile Gly 2970	Val Pro Gly
Ile Gly 2975	Val Pro Gly	Ile Gly 2980	Val Pro Gly	Ile Gly 2985	Val Pro Gly
Ile Gly 2990	Val Pro Gly	Ile Gly 2995	Val Pro Gly	Ile Gly 3000	Val Pro Gly
Ile Gly	Val Pro Gly	Ile Gly	Val Pro Gly	Ile Gly	Val Pro Gly

3005				3010				3015			
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Ile	Gly	Val	Pro
	3020				3025				3030		
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Ile	Gly	Val	Pro
	3035				3040				3045		
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Ile	Gly	Val	Pro
	3050				3055				3060		
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Ile	Gly	Val	Pro
	3065				3070				3075		
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Ile	Gly	Val	Pro
	3080				3085				3090		
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Ile	Gly	Val	Pro
	3095				3100				3105		
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Ile	Gly	Val	Pro
	3110				3115				3120		
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Ile	Gly	Val	Pro
	3125				3130				3135		
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Ile	Gly	Val	Pro
	3140				3145				3150		
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Ile	Gly	Val	Pro
	3155				3160				3165		
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Ile	Gly	Val	Pro
	3170				3175				3180		
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Ile	Gly	Val	Pro
	3185				3190				3195		
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Ile	Gly	Val	Pro
	3200				3205				3210		
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Ile	Gly	Val	Pro
	3215				3220				3225		
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Ile	Gly	Val	Pro
	3230				3235				3240		
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Ile	Gly	Val	Pro
	3245				3250				3255		
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Ile	Gly	Val	Pro
	3260				3265				3270		
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Ile	Gly	Val	Pro
	3275				3280				3285		
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Ile	Gly	Val	Pro
	3290				3295				3300		
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Ile	Gly	Val	Pro
	3305				3310				3315		
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Ile	Gly	Val	Pro
	3320				3325				3330		
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Ile	Gly	Val	Pro
	3335				3340				3345		
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Ile	Gly	Val	Pro
	3350				3355				3360		
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Ile	Gly	Val	Pro
	3365				3370				3375		
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Ile	Gly	Val	Pro
	3380				3385				3390		

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Ile Gly 3395	Val Pro Gly	Ile Gly 3400	Val Pro Gly	Ile Gly 3405	Val Pro Gly
Ile Gly 3410	Val Pro Gly	Ile Gly 3415	Val Pro Gly	Ile Gly 3420	Val Pro Gly
Ile Gly 3425	Val Pro Gly	Ile Gly 3430	Val Pro Gly	Ile Gly 3435	Val Pro Gly
Ile Gly 3440	Val Pro Gly	Ile Gly 3445	Val Pro Gly	Ile Gly 3450	Val Pro Gly
Ile Gly 3455	Val Pro Gly	Ile Gly 3460	Val Pro Gly	Ile Gly 3465	Val Pro Gly
Ile Gly 3470	Val Pro Gly	Ile Gly 3475	Val Pro Gly	Ile Gly 3480	Val Pro Gly
Ile Gly 3485	Val Pro Gly	Ile Gly 3490	Val Pro Gly	Ile Gly 3495	Val Pro Gly
Ile Gly 3500	Val Pro Gly	Ile Gly 3505	Val Pro Gly	Ile Gly 3510	Val Pro Gly
Ile Gly 3515	Val Pro Gly	Ile Gly 3520	Val Pro Gly	Ile Gly 3525	Val Pro Gly
Ile Gly 3530	Val Pro Gly	Ile Gly 3535	Val Pro Gly	Ile Gly 3540	Val Pro Gly
Ile Gly 3545	Val Pro Gly	Ile Gly 3550	Val Pro Gly	Ile Gly 3555	Val Pro Gly
Ile Gly 3560	Val Pro Gly	Ile Gly 3565	Val Pro Gly	Ile Gly 3570	Val Pro Gly
Ile Gly 3575	Val Pro Gly	Ile Gly 3580	Val Pro Gly	Ile Gly 3585	Val Pro Gly
Ile Gly 3590	Val Pro Gly	Ile Gly 3595	Val Pro Gly	Ile Gly 3600	Val Pro Gly
Ile Gly 3605	Val Pro Gly	Ile Gly 3610	Val Pro Gly	Ile Gly 3615	Val Pro Gly
Ile Gly 3620	Val Pro Gly	Ile Gly 3625	Val Pro Gly	Ile Gly 3630	Val Pro Gly
Ile Gly 3635	Val Pro Gly	Ile Gly 3640	Val Pro Gly	Ile Gly 3645	Val Pro Gly
Ile Gly 3650	Val Pro Gly	Ile Gly 3655	Val Pro Gly	Ile Gly 3660	Val Pro Gly
Ile Gly 3665	Val Pro Gly	Ile Gly 3670	Val Pro Gly	Ile Gly 3675	Val Pro Gly
Ile Gly 3680	Val Pro Gly	Ile Gly 3685	Val Pro Gly	Ile Gly 3690	Val Pro Gly
Ile Gly 3695	Val Pro Gly	Ile Gly 3700	Val Pro Gly	Ile Gly 3705	Val Pro Gly
Ile Gly 3710	Val Pro Gly	Ile Gly 3715	Val Pro Gly	Ile Gly 3720	Val Pro Gly
Ile Gly 3725	Val Pro Gly	Ile Gly 3730	Val Pro Gly	Ile Gly 3735	Val Pro Gly
Ile Gly 3740	Val Pro Gly	Ile Gly 3745	Val Pro Gly	Ile Gly 3750	Val Pro Gly
Ile Gly 3755	Val Pro Gly	Ile Gly 3760	Val Pro Gly	Ile Gly 3765	Val Pro Gly

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Ile Gly 3770	Val Pro Gly	Ile Gly 3775	Val Pro Gly	Ile Gly 3780	Val Pro Gly
Ile Gly 3785	Val Pro Gly	Ile Gly 3790	Val Pro Gly	Ile Gly 3795	Val Pro Gly
Ile Gly 3800	Val Pro Gly	Ile Gly 3805	Val Pro Gly	Ile Gly 3810	Val Pro Gly
Ile Gly 3815	Val Pro Gly	Ile Gly 3820	Val Pro Gly	Ile Gly 3825	Val Pro Gly
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Ile Gly 3845	Val Pro Gly	Ile Gly 3850	Val Pro Gly	Ile Gly 3855	Val Pro Gly
Ile Gly 3860	Val Pro Gly	Ile Gly 3865	Val Pro Gly	Ile Gly 3870	Val Pro Gly
Ile Gly 3875	Val Pro Gly	Ile Gly 3880	Val Pro Gly	Ile Gly 3885	Val Pro Gly
Ile Gly 3890	Val Pro Gly	Ile Gly 3895	Val Pro Gly	Ile Gly 3900	Val Pro Gly
Ile Gly 3905	Val Pro Gly	Ile Gly 3910	Val Pro Gly	Ile Gly 3915	Val Pro Gly
Ile Gly 3920	Val Pro Gly	Ile Gly 3925	Val Pro Gly	Ile Gly 3930	Val Pro Gly
Ile Gly 3935	Val Pro Gly	Ile Gly 3940	Val Pro Gly	Ile Gly 3945	Val Pro Gly
Ile Gly 3950	Val Pro Gly	Ile Gly 3955	Val Pro Gly	Ile Gly 3960	Val Pro Gly
Ile Gly 3965	Val Pro Gly	Ile Gly 3970	Val Pro Gly	Ile Gly 3975	Val Pro Gly
Ile Gly 3980	Val Pro Gly	Ile Gly 3985	Val Pro Gly	Ile Gly 3990	Val Pro Gly
Ile Gly 3995	Val Pro Gly	Ile Gly 4000	Val Pro Gly	Ile Gly 4005	Val Pro Gly
Ile Gly 4010	Val Pro Gly	Ile Gly 4015	Val Pro Gly	Ile Gly 4020	Val Pro Gly
Ile Gly 4025	Val Pro Gly	Ile Gly 4030	Val Pro Gly	Ile Gly 4035	Val Pro Gly
Ile Gly 4040	Val Pro Gly	Ile Gly 4045	Val Pro Gly	Ile Gly 4050	Val Pro Gly
Ile Gly 4055	Val Pro Gly	Ile Gly 4060	Val Pro Gly	Ile Gly 4065	Val Pro Gly
Ile Gly 4070	Val Pro Gly	Ile Gly 4075	Val Pro Gly	Ile Gly 4080	Val Pro Gly
Ile Gly 4085	Val Pro Gly	Ile Gly 4090	Val Pro Gly	Ile Gly 4095	Val Pro Gly
Ile Gly 4100	Val Pro Gly	Ile Gly 4105	Val Pro Gly	Ile Gly 4110	Val Pro Gly
Ile Gly 4115	Val Pro Gly	Ile Gly 4120	Val Pro Gly	Ile Gly 4125	Val Pro Gly
Ile Gly 4130	Val Pro Gly	Ile Gly 4135	Val Pro Gly	Ile Gly 4140	Val Pro Gly
Ile Gly	Val Pro Gly	Ile Gly	Val Pro Gly	Ile Gly	Val Pro Gly

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4145					4150					4155				
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly
4160					4165					4170				
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly
4175					4180					4185				
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly
4190					4195					4200				
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly
4205					4210					4215				
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly
4220					4225					4230				
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly
4235					4240					4245				
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly
4250					4255					4260				
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly
4265					4270					4275				
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly
4280					4285					4290				
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly
4295					4300					4305				
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly
4310					4315					4320				
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly
4325					4330					4335				
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly
4340					4345					4350				
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly
4355					4360					4365				
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly
4370					4375					4380				
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly
4385					4390					4395				
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly
4400					4405					4410				
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly
4415					4420					4425				
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly
4430					4435					4440				
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly
4445					4450					4455				
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly
4460					4465					4470				
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly
4475					4480					4485				
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly
4490					4495					4500				
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly
4505					4510					4515				
Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly	Ile	Gly	Val	Pro	Gly
4520					4525					4530				

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Ile Gly 4535	Val Pro Gly	Ile Gly 4540	Val Pro Gly	Ile Gly 4545	Val Pro Gly
Ile Gly 4550	Val Pro Gly	Ile Gly 4555	Val Pro Gly	Ile Gly 4560	Val Pro Gly
Ile Gly 4565	Val Pro Gly	Ile Gly 4570	Val Pro Gly	Ile Gly 4575	Val Pro Gly
Ile Gly 4580	Val Pro Gly	Ile Gly 4585	Val Pro Gly	Ile Gly 4590	Val Pro Gly
Ile Gly 4595	Val Pro Gly	Ile Gly 4600	Val Pro Gly	Ile Gly 4605	Val Pro Gly
Ile Gly 4610	Val Pro Gly	Ile Gly 4615	Val Pro Gly	Ile Gly 4620	Val Pro Gly
Ile Gly 4625	Val Pro Gly	Ile Gly 4630	Val Pro Gly	Ile Gly 4635	Val Pro Gly
Ile Gly 4640	Val Pro Gly	Ile Gly 4645	Val Pro Gly	Ile Gly 4650	Val Pro Gly
Ile Gly 4655	Val Pro Gly	Ile Gly 4660	Val Pro Gly	Ile Gly 4665	Val Pro Gly
Ile Gly 4670	Val Pro Gly	Ile Gly 4675	Val Pro Gly	Ile Gly 4680	Val Pro Gly
Ile Gly 4685	Val Pro Gly	Ile Gly 4690	Val Pro Gly	Ile Gly 4695	Val Pro Gly
Ile Gly 4700	Val Pro Gly	Ile Gly 4705	Val Pro Gly	Ile Gly 4710	Val Pro Gly
Ile Gly 4715	Val Pro Gly	Ile Gly 4720	Val Pro Gly	Ile Gly 4725	Val Pro Gly
Ile Gly 4730	Val Pro Gly	Ile Gly 4735	Val Pro Gly	Ile Gly 4740	Val Pro Gly
Ile Gly 4745	Val Pro Gly	Ile Gly 4750	Val Pro Gly	Ile Gly 4755	Val Pro Gly
Ile Gly 4760	Val Pro Gly	Ile Gly 4765	Val Pro Gly	Ile Gly 4770	Val Pro Gly
Ile Gly 4775	Val Pro Gly	Ile Gly 4780	Val Pro Gly	Ile Gly 4785	Val Pro Gly
Ile Gly 4790	Val Pro Gly	Ile Gly 4795	Val Pro Gly	Ile Gly 4800	Val Pro Gly
Ile Gly 4805	Val Pro Gly	Ile Gly 4810	Val Pro Gly	Ile Gly 4815	Val Pro Gly
Ile Gly 4820	Val Pro Gly	Ile Gly 4825	Val Pro Gly	Ile Gly 4830	Val Pro Gly
Ile Gly 4835	Val Pro Gly	Ile Gly 4840	Val Pro Gly	Ile Gly 4845	Val Pro Gly
Ile Gly 4850	Val Pro Gly	Ile Gly 4855	Val Pro Gly	Ile Gly 4860	Val Pro Gly
Ile Gly 4865	Val Pro Gly	Ile Gly 4870	Val Pro Gly	Ile Gly 4875	Val Pro Gly
Ile Gly 4880	Val Pro Gly	Ile Gly 4885	Val Pro Gly	Ile Gly 4890	Val Pro Gly
Ile Gly 4895	Val Pro Gly	Ile Gly 4900	Val Pro Gly	Ile Gly 4905	Val Pro Gly

Ile Gly
5000

<400> SEQUENCE: 10

Val Gly Val Pro Gly Val Gly Val Pro Gly Val Gly Val Pro Gly Val

<400> SEQUENCE: 11

Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	1
				5					10					15		
Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	
			20					25					30			
Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	
		35					40					45				
Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	
	50					55					60					
Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	
65					70					75					80	
Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	
				85					90					95		

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Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val
100 105 110

Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro
115 120 125

Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly
130 135 140

Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala
145 150 155 160

Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly
165 170 175

Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val
180 185 190

Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro
195 200 205

Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly
210 215 220

Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala
225 230 235 240

Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly
245 250 255

Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val
260 265 270

Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro
275 280 285

Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly
290 295 300

Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala
305 310 315 320

Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly
325 330 335

Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val
340 345 350

Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro
355 360 365

Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly
370 375 380

Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala
385 390 395 400

Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly
405 410 415

Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val
420 425 430

Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro
435 440 445

Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly
450 455 460

Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala
465 470 475 480

Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly
485 490 495

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Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	
			500					505					510			
Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	
		515					520					525				
Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	
		530					535					540				
Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	
		545					550					555				560
Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	
				565					570					575		
Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	
			580					585					590			
Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	
		595					600					605				
Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	
		610					615					620				
Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	
		625					630					635				640
Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	
				645					650					655		
Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	
			660					665					670			
Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	
		675					680					685				
Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	
		690					695					700				
Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	
		705					710					715				720
Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	
				725					730					735		
Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	
			740					745					750			
Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	
		755					760					765				
Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	
		770					775					780				
Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	
		785					790					795				800
Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	
				805					810					815		
Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	
			820					825					830			
Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	
		835					840					845				
Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	
		850					855					860				
Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	
		865					870					875				880
Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	
				885					890					895		
Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	Pro	Gly	Ala	Gly	Val	

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900	905	910
Pro Gly Ala Gly Val 915	Pro Gly Ala Gly Val 920	Pro Gly Ala Gly Val Pro 925
Gly Ala Gly Val Pro 930	Gly Ala Gly Val Pro 935	Gly Ala Gly Val Pro Gly 940
Ala Gly Val Pro Gly 945	Ala Gly Val Pro Gly 950	Ala Gly Val Pro Gly Ala 955 960

Gly Tyr

<210> SEQ ID NO 12

<211> LENGTH: 962

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 12

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Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val 20 25 30
Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro 35 40 45
Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly 50 55 60
Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala 65 70 75 80
Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly 85 90 95
Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val 100 105 110
Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro 115 120 125
Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly 130 135 140
Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala 145 150 155 160
Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly 165 170 175
Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val 180 185 190
Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro 195 200 205
Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly 210 215 220
Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala 225 230 235 240
Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly 245 250 255
Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val 260 265 270
Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro

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275	280	285
Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly		
290	295	300
Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala		
305	310	315
Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly		
	325	330
		335
Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val		
	340	345
		350
Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro		
	355	360
		365
Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly		
	370	375
		380
Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala		
385	390	395
		400
Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly		
	405	410
		415
Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val		
	420	425
		430
Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro		
	435	440
		445
Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly		
	450	455
		460
Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala Gly Val Pro Gly Ala		
465	470	475
		480
Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly		
	485	490
		495
Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val		
	500	505
		510
Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro		
	515	520
		525
Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly		
	530	535
		540
Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile		
545	550	555
		560
Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly		
	565	570
		575
Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val		
	580	585
		590
Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro		
	595	600
		605
Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly		
	610	615
		620
Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile		
625	630	635
		640
Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly		
	645	650
		655
Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val		
	660	665
		670
Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro		
	675	680
		685

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Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly
 690 695 700
 Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile
 705 710 715 720
 Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly
 725 730 735
 Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val
 740 745 750
 Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro
 755 760 765
 Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly
 770 775 780
 Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile
 785 790 795 800
 Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly
 805 810 815
 Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val
 820 825 830
 Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro
 835 840 845
 Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly
 850 855 860
 Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile
 865 870 875 880
 Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly
 885 890 895
 Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val
 900 905 910
 Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro
 915 920 925
 Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly
 930 935 940
 Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile Gly Val Pro Gly Ile
 945 950 955 960
 Gly Tyr

<210> SEQ ID NO 13
 <211> LENGTH: 244
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 polypeptide

<400> SEQUENCE: 13

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 Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
 20 25 30
 Asn Met His Trp Val Lys Gln Thr Pro Gly Arg Gly Leu Glu Trp Ile
 35 40 45
 Gly Ala Ile Tyr Pro Gly Asn Gly Asp Thr Ser Tyr Asn Gln Lys Phe
 50 55 60

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Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
 65 70 75 80
 Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Ser Thr Tyr Tyr Gly Gly Asp Trp Tyr Phe Asn Val Trp Gly
 100 105 110
 Ala Gly Thr Thr Val Thr Val Ser Ala Gly Gly Gly Gly Ser Gly Gly
 115 120 125
 Gly Gly Ser Gly Gly Gly Gly Ser Gln Ile Val Leu Ser Gln Ser Pro
 130 135 140
 Ala Ile Leu Ser Ala Ser Pro Gly Glu Lys Val Thr Met Thr Cys Arg
 145 150 155 160
 Ala Ser Ser Ser Val Ser Tyr Ile His Trp Phe Gln Gln Lys Pro Gly
 165 170 175
 Ser Ser Pro Lys Pro Trp Ile Tyr Ala Thr Ser Asn Leu Ala Ser Gly
 180 185 190
 Val Pro Val Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu
 195 200 205
 Thr Ile Ser Arg Val Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln
 210 215 220
 Gln Trp Thr Ser Asn Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu
 225 230 235 240
 Ile Lys Arg Thr

<210> SEQ ID NO 14
 <211> LENGTH: 2500
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 polypeptide
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 <222> LOCATION: (1)..(2500)
 <223> OTHER INFORMATION: This sequence may encompass 1 to 500 "VPGXG"
 repeats
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (4)..(4)
 <223> OTHER INFORMATION: Any amino acid
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<223> OTHER INFORMATION: Any amino acid
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<222> LOCATION: (39)..(39)
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<223> OTHER INFORMATION: Any amino acid
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<223> OTHER INFORMATION: Any amino acid
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130 135 140
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340 345 350
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1. A recombinant polypeptide comprising an elastin-like peptide (ELP) fused to a scFv, or a biological equivalent of the scFv.

2. The recombinant polypeptide of claim 1, wherein the scFv is fused to the N-terminus of ELP.

3. The polypeptide of claim 1 or 2, wherein the scFv is the single chain variable region of the anti-CD20 antibody.

4. The polypeptide of claim 2, wherein the sequence of the polypeptide corresponds to a sequence selected from the group consisting of: SEQ ID NOS: 3, 4, and 5 or a biological equivalent thereof.

5. The polypeptide of claim 1, wherein the ELP comprises the primary sequence of SEQ ID NO. 6, wherein X is any amino acid and n is an integer from 1 to about 500 (SEQ ID NO: 14).

6. The polypeptide of claim 1, wherein the ELP comprises the primary sequence of SEQ ID NO: 7, wherein n is an integer from 1 to about 500.

7. The polypeptide of claim 1, wherein the ELP consists essentially of the primary sequence of SEQ ID NO: 6,

wherein X is any amino acid (Repeat sequences of SEQ NO: 6 wherein n is an integer from 1 to about 500 is disclosed as SEQ ID NO:

14) or SEQ ID NO: 7, wherein n is an integer from 1 to about 500.

8. The polypeptide of claim 1 further comprising a detectable label.

9. The polypeptide of claim 3, wherein the scFv comprises the sequence of SEQ ID NO: 1 or SEQ ID NO: 2 or a biological equivalent thereof.

10. The polypeptide of claim 1 linked to a therapeutic agent.

11. The polypeptide of claim 10, wherein the therapeutic agent is an anti-cancer drug.

12. A nucleotide encoding the polypeptide of claim 1.

13. A vector and/or host cell comprising the polynucleotide of claim 12.

14. A composition comprising at least two polypeptides of claim 1.

15. The composition of claim **14**, wherein the at least two polypeptides are organized into a cylindrical particle.

16. The composition of claim **15**, wherein the cylindrical particle has a core.

17. The composition of claim **16**, wherein the core of the cylindrical particle comprises an scFv is fused to a N-terminus of an ELP.

18. The composition of claim **14**, wherein the at least two polypeptides are organized into a spherical particle or a nano-worm.

19. The composition of claim **18**, wherein the particle has a core.

20. The composition of claim **19**, wherein the core of the particle comprises an scFv is fused to a N-terminus of an ELP.

21. A composition comprising a carrier and the polypeptide of claim **1**.

22. A method for preparing a therapeutic polypeptide, comprising expressing the polynucleotide of claim **12** in a suitable expression system.

23. The method of claim **22**, further comprising separating or purifying the polypeptide from the expression system.

24. The method of claim **23**, further comprising denaturing and refolding the polypeptide.

25. The method of claim **24**, wherein the denaturing and refolding is performed at least twice.

26. A method for inducing apoptosis of a CD20+ cell comprising contacting the cell with an effective amount of the polypeptide of claim **3**.

27. The method of claim **26**, wherein the contacting is to a cell in vitro or in vivo.

28. The method of claim **26**, wherein the cell is a malignant B-cell.

29. A method for treating a CD20-related disease or disorder, comprising administering to a patient in need of such treatment the polypeptide of claim **3**.

30. The method of claim **29**, wherein the CD20-related disease or disorder is cancer or an autoimmune disease.

31. A kit for treating a CD20-related disease or disorder or inducing apoptosis of a CD20+ cell, comprising the polypeptide of claim **3**.

32. A method for targeting a scFv-ELP to a cell expressing CD20 comprising contacting the cell with an effective amount of the polypeptide of claim **1**, wherein the scFv component of the scFv-ELP binds to the CD20 receptor on the cell.

33. The method of claim **32** wherein the contacting is to a cell in vitro or in vivo.

34. The method of claim **33** wherein the scFv-ELP is linked to a therapeutic agent.

* * * * *