FVIII PEPTIDES FOR IMMUNE TOLERANCE INDUCTION AND IMMUNODIAGNOSTICS

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] The present application claims priority to U.S. Provisional Patent Application Serial Number 61/407,402, filed on October 27, 2010, U.S. Provisional Patent Application Serial Number 61/467,894, filed on March 25, 2011, and U.S. Provisional Patent Application Serial Number 61/502,476, filed on June 29, 2011, the disclosures of which are hereby incorporated by reference in their entireties for all purposes.

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0002] NOT APPLICABLE

REFERENCE TO A "SEQUENCE LISTING," A TABLE, OR A COMPUTER PROGRAM LISTING APPENDIX SUBMITTED ON A COMPACT DISK

[0003] NOT APPLICABLE

BACKGROUND OF THE INVENTION

[0004] Factor VIII (FVIII) is a protein found in blood plasma that acts as a cofactor in the cascade of reactions leading to blood coagulation. Hemophilia A is caused by a reduction or deficiency of functional FVIII protein and is one of the most common bleeding disorders that affects about 1 in 5000-10000 men. Clinical symptoms in hemophilia are frequent muscle and joint bleeds, and trauma can even lead to life threatening situations. Currently, effective treatments for hemophilia include replacing the missing FVIII protein using intravenous application of recombinant or plasma derived FVIII products. Such preparations are generally administered either in response to a bleeding episode (on-demand therapy) or at frequent, regular

intervals to prevent uncontrolled bleeding (prophylaxis). Unfortunately, the appearance of neutralizing anti-FVIII antibodies (FVIII inhibitors) is a major complication during replacement therapy with FVIII products. Approximately 25% of the patients receiving treatment develop this immunity to FVIII protein, thus making further control of bleeding very difficult.

[0005] The cause for this immune response to FVIII protein has not been fully elucidated, but the specifics of a patient's immune system can affect their response to therapy. Normally, the immune system develops a tolerance to certain antigens, e.g., "self" antigens. This feature is important because, otherwise, if a self antigen is recognized as a foreign antigen, autoimmune disease results. Hemophilia A patients, in particular, have a genetic defect in their FVIII gene, which causes the immune system to not recognize the administered FVIII protein as a "self" antigen. Thus, when FVIII protein is administered during coagulation factor replacement therapy, the patient's immune system recognizes the FVIII protein as a foreign antigen or an altered self protein and develops anti-FVIII antibodies accordingly.

[0006] The FVIII inhibitors, i.e., anti-FVIII antibodies are produced by plasma cells derived from FVIII specific B cells. B cells need the help of activated $CD4^+$ T-cells to proliferate and differentiate into anti-FVIII antibody producing plasma cells. For example, FVIII protein is recognized by B and T lymphocytes in different ways. The induction of anti-FVIII antibodies is T helper cell dependent. B cells recognize whole protein epitopes via their specific B cell receptor. T-cells on the other hand, recognize proteins in the form of processed peptides complexed with an MHC class II molecule presented on the surface of an antigen presenting cell. Each $CD4^+$ T-cell clone recognizes only one specific peptide-MHC complex. For presenting the peptides to the T-cells, MHC class II molecules have an open binding groove that allows peptides of various lengths to fit in and be presented on the surface of a cell. Moreover, the MHC class II protein contains four binding pockets that differ for the various haplotypes (Jones *et al.*, *Nature Rev. Immunol.* 6:271-282 (2006)). Only specific amino acids fit into these binding pockets, and the minimal size of binding peptides is nine amino acids. Notably, different MHC class II haplotypes can present different peptides. Thus, it is likely that a patient's MHC class II haplotype influences the risk of developing anti-FVIII antibodies. Indeed, several studies have shown that there is a correlation of the human MHC class II haplotype HLA-DRB1*1501 with an increased risk for anti-FVIII antibody development (Pavlova *et al.*, *J. Thromb. Haemost.* 7:2006-2015 (2009); Oldenburg *et al.*, *Thromb. Haemost.* 77:238-242 (1997); Hay *et al.*, *Thromb. Haemost.* 77:234-237 (1997)).

[0007] Certain approaches have been explored to address the challenges associated with treating hemophilia by administration of FVIII protein. For example, WO 03/087161 discloses modified FVIII proteins, in which the immune characteristics of the FVIII protein are modified by reducing or removing the number of potential T-cell epitopes present on the protein. A number of regions that include T-cell epitopes along the FVIII protein were identified, including, e.g., $FVIII^{2030-2044}$. According to the disclosure, removal of such regions could be used to provide functional FVIII protein that did not induce production of anti-FVIII antibodies. WO 09/071886 also discloses specific regions of FVIII protein that were predicted to give rise to HLA-DR2 binding peptides that are involved in a patient's immune response, such as, e.g., $FVIII^{475-495}$, $FVIII^{542-562}$, $FVIII^{1785-1805}$, and $FVIII^{2158-2178}$. The peptides were identified for possible use in inducing immune tolerance in a patient.

[0008] While there have been advances in identifying regions of FVIII protein involved in the immune response, there is still a need to identify other regions of FVIII protein that can be used for developing other therapeutic peptides and methodologies that can, for example, be used to treat patients having hemophilia A.

BRIEF SUMMARY OF THE INVENTION

[0009] The present invention is based on the identification of regions of FVIII protein related to the immune response against FVIII molecules. More specifically, a FVIII peptide including the region of FVIII protein can be used to induce tolerance to human FVIII in patients with, e.g., hemophilia A. Furthermore, the FVIII peptides can be used for immunodiagnostic purposes to monitor patients with hemophilia A during replacement therapy and during immune tolerance induction therapy.

[0010] In one aspect, the present invention provides a method of inducing an immune tolerance to FVIII in a subject in need thereof, the method comprising a step of: administering to the subject a therapeutically effective amount of a peptide having an amino acid sequence consisting of: $(R^1)_x$-P-$(R^2)_y$, wherein: P is an amino acid sequence having at least 85% identity to at least nine consecutive amino acids of a sequence selected from SEQ ID NOS:10, 68, 344, and 740; R^1 is an amino acid sequence consisting of from 1 to 80 amino acids; R^2 is an amino acid sequence consisting of from 1 to 80 amino acids; and each of x and y are independently zero or one.

[0011] In one embodiment of the methods provided above, P is an amino acid sequence having at least 90% identity to a sequence of at least nine consecutive amino acids of SEQ ID NO:10.

[0012] In one embodiment of the methods provided above, P is an amino acid sequence identical to a sequence of at least nine consecutive amino acids of SEQ ID NO:10.

[0013] In one embodiment of the methods provided above, P is an amino acid sequence having at least 90% identity to a sequence of at least nine consecutive amino acids of SEQ ID NO:68.

[0014] In one embodiment of the methods provided above, P is an amino acid sequence having at least 95% identity to a sequence of at least nine consecutive amino acids of SEQ ID NO:68.

[0015] In one embodiment of the methods provided above, P is an amino acid sequence identical to a sequence of at least nine consecutive amino acids of SEQ ID NO:68.

[0016] In one embodiment of the methods provided above, P is an amino acid sequence having at least 85% identity to a sequence of at least nine consecutive amino acids of SEQ ID NO:344.

[0017] In one embodiment of the methods provided above, P is an amino acid sequence having at least 90% identity to a sequence of at least nine consecutive amino acids of SEQ ID NO:344.

[0018] In one embodiment of the methods provided above, P is an amino acid sequence having at least 95% identity to a sequence of at least nine consecutive amino acids of SEQ ID NO:344.

[0019] In one embodiment of the methods provided above, P is an amino acid sequence identical to a sequence of at least nine consecutive amino acids of SEQ ID NO:344.

[0020] In one embodiment of the methods provided above, P is an amino acid sequence having at least 85% identity to a sequence of at least nine consecutive amino acids of SEQ ID NO:740.

[0021] In one embodiment of the methods provided above, P is an amino acid sequence having at least 90% identity to a sequence of at least nine consecutive amino acids of SEQ ID NO:740.

[0022] In one embodiment of the methods provided above, P is an amino acid sequence having at least 95% identity to a sequence of at least nine consecutive amino acids of SEQ ID NO:740.

[0023] In one embodiment of the methods provided above, P is an amino acid sequence identical to a sequence of at least nine consecutive amino acids of SEQ ID NO:740.

[0024] In one embodiment of the methods provided above, x and y are both zero.

[0025] In one embodiment of the methods provided above, x is one and y is zero.

[0026] In one embodiment of the methods provided above, x is zero and y is one.

[0027] In one embodiment of the methods provided above, x and y are both zero.

[0028] In one embodiment of the methods provided above, the peptide consists of from 9 to 100 amino acids.

[0029] In one embodiment of the methods provided above, the peptide consists of from 9 to 50 amino acids.

[0030] In one embodiment of the methods provided above, the peptide consists of from 9 to 25 amino acids.

[0031] In one embodiment of the methods provided above, administration of the pharmaceutical composition prevents development of anti-FVIII antibodies in the subject.

[0032] In one embodiment of the methods provided above, administration of the pharmaceutical composition reduces an amount anti-FVIII antibodies present in the subject.

[0033] In one aspect, the present invention provides a peptide consisting of the amino acid sequence: $(R^1)_x$-P-$(R^2)_y$, wherein: P is an amino acid sequence having at least 85% identity to a sequence of at least nine consecutive amino acids of a sequence selected from SEQ ID NOS:10, 68, 159, 250, 344, 477, 568, 659, and 740; R^1 is an amino acid sequence consisting of from 1 to 80 amino acids; R^2 is an amino acid sequence consisting of from 1 to 80 amino acids; and each of x and y are independently zero or one.

[0034] In one embodiment of the peptides provided above, P is an amino acid sequence having at least 90% identity to a sequence of at least nine consecutive amino acids of SEQ ID NO:10.

[0035] In one embodiment of the peptides provided above, P is an amino acid sequence identical to a sequence of at least nine consecutive amino acids of SEQ ID NO:10.

[0036] In one embodiment of the peptides provided above, P is an amino acid sequence having at least 90% identity to a sequence of at least nine consecutive amino acids of SEQ ID NO:68.

[0037] In one embodiment of the peptides provided above, P is an amino acid sequence having at least 95% identity to a sequence of at least nine consecutive amino acids of SEQ ID NO:68.

[0038] In one embodiment of the peptides provided above, P is an amino acid sequence identical to a sequence of at least nine consecutive amino acids of SEQ ID NO:68.

[0039] In one embodiment of the peptides provided above, P is an amino acid sequence having at least 85% identity to a sequence of at least nine consecutive amino acids of SEQ ID NO:344.

[0040] In one embodiment of the peptides provided above, P is an amino acid sequence having at least 90% identity to a sequence of at least nine consecutive amino acids of SEQ ID NO:344.

[0041] In one embodiment of the peptides provided above, P is an amino acid sequence having at least 95% identity to a sequence of at least nine consecutive amino acids of SEQ ID NO:344.

[0042] In one embodiment of the peptides provided above, P is an amino acid sequence identical to a sequence of at least nine consecutive amino acids of SEQ ID NO:344.

[0043] In one embodiment of the peptides provided above, P is an amino acid sequence having at least 85% identity to a sequence of at least nine consecutive amino acids of SEQ ID NO:740.

[0044] In one embodiment of the peptides provided above, P is an amino acid sequence having at least 90% identity to a sequence of at least nine consecutive amino acids of SEQ ID NO:740.

[0045] In one embodiment of the peptides provided above, P is an amino acid sequence having at least 95% identity to a sequence of at least nine consecutive amino acids of SEQ ID NO:740.

[0046] In one embodiment of the peptides provided above, P is an amino acid sequence identical to a sequence of at least nine consecutive amino acids of SEQ ID NO:740.

[0047] In one embodiment of the peptides provided above, x and y are both zero.

[0048] In one embodiment of the peptides provided above, x is one and y is zero.

[0049] In one embodiment of the peptides provided above, x is zero and y is one.

[0050] In one embodiment of the peptides provided above, x and y are both zero.

[0051] In one embodiment of the peptides provided above, the peptide consists of from 9 to 100 amino acids.

[0052] In one embodiment of the peptides provided above, the peptide consists of from 9 to 50 amino acids.

[0053] In one embodiment of the peptides provided above, the peptide consists of from 9 to 25 amino acids.

[0054] In one aspect, the present invention provides a composition comprising a peptide as described herein.

[0055] In one embodiment of the compositions provided above, the composition is formulated for pharmaceutical administration.

[0056] In one embodiment of the compositions provided above, the composition further comprises a second polypeptide, the second polypeptide consisting of the amino acid sequence: $(R^1)_x$-P-$(R^2)_y$, wherein: P is an amino acid sequence having at least 85% identity to a sequence of at least nine consecutive amino acids of a sequence selected from SEQ ID NOS:10, 68, 159, 250, 477, 568, 659, and 740; R^1 is an amino acid sequence consisting of from 1 to 80 amino acids; R^2 is an amino acid sequence consisting of from 1 to 80 amino acids; and each of x and y are independently zero or one.

[0057] In one aspect, the present invention provides a method of making a FVIII peptide, the method comprising the steps of: a) providing a culture of cells comprising a polynucleotide that encodes a FVIII peptide according to any one of claims 24 to 41; and b) expressing the peptide in the culture of cells.

[0058] In one aspect, the present invention provides a method of identifying a FVIII peptide-specific T cell, the method comprising: a) combining a plurality of CD4+ T cells with a peptide complexed with a MHC class II multimer, wherein the peptide is a FVIII peptide according to any one of claims 24 to 41; and b) identifying at least one of the members of the plurality of CD4+ T cells that is specific for the peptide complexed with the MHC class II multimer.

[0059] In one embodiment of the methods provided above, the MHC class II multimer is a MHC class II tetramer.

[0060] In one embodiment of the methods provided above, the peptide or MHC class II multimer further comprises a detectable moiety.

[0061] In one embodiment of the methods provided above, the method further comprises isolating at least one CD4+ T cell that is specific for the peptide.

[0062] In one embodiment of the methods provided above, the CD4+ T cell is isolated using flow cytometry.

[0063] In one aspect, the present invention provides a fusion protein comprising a FVIII peptide as provided herein and a second peptide.

[0064] In one embodiment of the methods provided above, the second peptide is a reporter peptide.

[0065] In one embodiment of the methods provided above, the fusion protein is encoded by a nucleic acid.

[0066] In one embodiment of the methods provided above, the FVIII peptide is chemically linked to the second peptide.

[0067] In one aspect, the FVIII peptides provided herein are used to induce immune tolerance towards human FVIII for the prevention of FVIII inhibitor development.

[0068] In one aspect, the FVIII peptides provided herein are used to induce tolerance towards human FVIII for the treatment of patients with established FVIII inhibitors.

[0069] In one aspect, the FVIII peptides provided herein are used to generate reagents suitable for direct staining of FVIII specific T cells (*e.g.*, MHC class II multimers or MHC class II tetramers) in immune monitoring of patients during replacement therapy or during immune tolerance induction therapy.

[0070] In one aspect, the FVIII peptides provided herein are used to identify antigen specific T cells. In one embodiment, these reagents can be used to track FVIII specific T cells in *in vitro* and in *ex vivo* settings. In another embodiment, these reagents can be used to isolate and further characterize FVIII specific T cells. In one embodiment, fluorescent activated cell sorting (FACS) or single cell PCR can be used for these purposes.

[0071] In one aspect, the FVIII peptides provided herein are used for immune monitoring of FVIII specific T cells during immune tolerance induction therapy.

[0072] In one aspect, the FVIII peptides provided herein are used for immune monitoring of FVIII specific T cells during FVIII treatment.

[0073] In one aspect, the FVIII peptides provided herein are used for immunodiagnostics of FVIII specific T cells during clinical development of new immune modulators for the prevention of FVIII inhibitors.

BRIEF DESCRIPTION OF THE DRAWINGS

[0074] Not applicable.

DETAILED DESCRIPTION OF THE INVENTION

I. Introduction

[0075] The present invention is related to Factor VIII (FVIII) peptides that can be used to induce tolerance to FVIII protein in, for example, patients with hemophilia A. Furthermore, the peptides can be used for immunodiagnostic purposes to monitor FVIII-specific T cells in patients with hemophilia A during replacement therapy and during immune tolerance induction therapy.

[0076] The present invention is based in-part on the discovery that several regions of FVIII, specifically $FVIII^{102-122}$, $FVIII^{246-266}$, and $FVIII^{1401-1424}$, are involved in the immune response mounted against FVIII protein during Factor VIII replacement therapy or connected with acquired hemophilia. The amino acid sequences of the regions identified are TVVITLKNMASHPVSLHAVGV (SEQ ID NO:740), AWPKMHTVNGYVNRSLPGLIG (SEQ ID NO:68), and QANRSPLPIAKVSSFPSIRPIYLT (SEQ ID NO:344), respectively. It is believed that the present invention provides for the first time identification of these FVIII protein regions and their relationship to the immune response to FVIII protein.

[0077] Peptides of the present invention include peptides having at least a portion of the regions $FVIII^{102-122}$, $FVIII^{246-266}$, and $FVIII^{1401-1424}$ that complexes with a MHC class II molecule to produce a T cell epitope capable of being recognized by T cells involved in a patient's immune response. In some embodiments, the peptides include at least nine contiguous amino acids that correspond to nine contiguous amino acids in $FVIII^{102-122}$, $FVIII^{246-266}$, or $FVIII^{1401-1424}$. As described further below, the peptides provided herein also include peptides longer than nine amino acids in length as well as variants of the $FVIII^{102-122}$, $FVIII^{246-266}$, and $FVIII^{1401-1424}$ sequences. Such an identification of the peptides of the present invention can have implications

in improving and advancing therapeutic strategies designed to treat diseases related to blood coagulation, such as hemophilia A.

II. Definitions

[0078] The term "Factor VIII protein" or "FVIII protein" refers to any FVIII molecule which has at least a portion of the B domain intact, and which exhibits biological activity that is associated with native human FVIII protein. The FVIII molecule can be full-length FVIII. The FVIII molecule may also be a conservatively modified variant of native FVIII. The FVIII protein can be derived from human plasma or be produced by recombinant engineering techniques. Additional characterization of FVIII protein can be, e.g., found at paragraphs [0042]-[0055] in US 2010/0168018, which is incorporated by reference herein.

[0079] The term "Factor VIII peptide" or "FVIII peptide" refers to the peptides described herein that include an amino acid sequence corresponding to a region of FVIII protein discovered to be important in an immune response against FVIII. A FVIII peptide includes at least nine amino acids that complex with a MHC class II protein for presentation to T cells involved in the immune response. Additional amino acids can be present on either end of the at least nine amino acid core of the peptide. In some embodiments, a FVIII peptide can include a sequence identical to the particular region of native human FVIII protein. In other embodiments, a FVIII peptide can be a conservatively modified variant of a region of FVIII protein. As described further herein, a FVIII peptide can be characterized by a certain percent identity, e.g., 85% identical, relative to the sequence of a region of native human FVIII protein.

[0080] The term "amino acid" refers to naturally occurring and non-natural amino acids, including amino acid analogs and amino acid mimetics that function in a manner similar to the naturally occurring amino acids. Naturally occurring amino acids include those encoded by the genetic code, as well as those amino acids that are later modified, e.g., hydroxyproline, y-carboxyglutamate, and O-phosphoserine. Naturally occurring amino acids can include, e.g., D- and L-amino acids. The amino acids used herein can also include non-natural amino acids. Amino acid analogs refer to compounds that have the same basic chemical structure as a naturally occurring amino acid, i.e., any carbon that is bound to a hydrogen, a carboxyl group, an amino group, and an R group, e.g., homoserine, norleucine, methionine sulfoxide, or methionine methyl sulfonium. Such analogs have modified R groups (e.g., norleucine) or modified peptide backbones, but retain the same basic chemical structure as a naturally occurring amino acid.

Amino acid mimetics refer to chemical compounds that have a structure that is different from the general chemical structure of an amino acid, but that function in a manner similar to a naturally occurring amino acid. Amino acids may be referred to herein by either their commonly known three letter symbols or by the one-letter symbols recommended by the IUPAC-IUB Biochemical Nomenclature Commission. Nucleotides, likewise, may be referred to by their commonly accepted single-letter codes.

[0081] "Conservatively modified variants" applies to both amino acid and nucleic acid sequences. With respect to particular nucleic acid sequences, conservatively modified variants refers to those nucleic acids which encode identical or essentially identical amino acid sequences, or where the nucleic acid does not encode an amino acid sequence, to essentially identical sequences. Because of the degeneracy of the genetic code, a large number of functionally identical nucleic acids encode any given peptide. For instance, the codons GCA, GCC, GCG and GCU all encode the amino acid alanine. Thus, at every position where an alanine is specified by a codon, the codon can be altered to any of the corresponding codons described without altering the encoded polypeptide. Such nucleic acid variations are "silent variations," which are one species of conservatively modified variations. Every nucleic acid sequence herein which encodes a polypeptide also describes every possible silent variation of the nucleic acid. One of ordinary skill in the art will recognize that each codon in a nucleic acid (except AUG, which is ordinarily the only codon for methionine, and TGG, which is ordinarily the only codon for tryptophan) can be modified to yield a functionally identical molecule. Accordingly, each silent variation of a nucleic acid which encodes a polypeptide is implicit in each described sequence with respect to the expression product, but not with respect to actual probe sequences.

[0082] As to amino acid sequences, one of ordinary skill in the art will recognize that individual substitutions, deletions or additions to a nucleic acid or peptide sequence that alters, adds or deletes a single amino acid or a small percentage of amino acids in the encoded sequence is a "conservatively modified variant" where the alteration results in the substitution of an amino acid with a chemically similar amino acid. Conservative substitution tables providing functionally similar amino acids are well known in the art. Such conservatively modified variants are in addition to and do not exclude polymorphic variants, interspecies homologs, and alleles of the invention.

[0083] The following eight groups each contain amino acids that are conservative substitutions for one another: 1) Alanine (A), Glycine (G); 2) Aspartic acid (D), Glutamic acid (E); 3) Asparagine (N), Glutamine (Q); 4) Arginine (R), Lysine (K); 5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V); 6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W); 7) Serine (S), Threonine (T); and 8) Cysteine (C), Methionine (M). *See, e.g.*, Creighton, *Proteins* (1984).

[0084] The terms "identical" or percent "identity," in the context of two or more nucleic acids or peptide sequences, refer to two or more sequences or subsequences that are the same or have a specified percentage of amino acid residues or nucleotides that are the same (i.e., about 60% identity, preferably 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or higher identity over a specified region, when compared and aligned for maximum correspondence over a comparison window or designated region) as measured using a BLAST or BLAST 2.0 sequence comparison algorithms with default parameters described below, or by manual alignment and visual inspection.

[0085] By "therapeutically effective amount or dose" or "sufficient amount or dose" herein is meant a dose that produces effects for which it is administered. The exact dose will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (*see, e.g.*, Augsburger & Hoag, *Pharmaceutical Dosage Forms* (vols. 1-3, 3rd Ed. 2008); Lloyd, *The Art, Science and Technology of Pharmaceutical Compounding* (3rd Ed., 2008); Pickar, *Dosage Calculations* (8th Ed., 2007); and *Remington: The Science and Practice of Pharmacy*, 21st Ed., 2005, Gennaro, Ed., Lippincott, Williams & Wilkins).

III. FVIII Peptides

[0086] The present invention relates to FVIII peptides that correspond to regions of FVIII protein involved in an immune response against FVIII. In one aspect, the present invention provides a FVIII peptide consisting of a consecutive sequence of nine amino acids that is at least 85 % identical to nine consecutive amino acids in one of the following amino acid sequences: AWPKMHTVNGYVNRSLPGLIG (SEQ ID NO:68); QANRSPLPIAKVSSFPSIRPIYLT (SEQ ID NO:344); or TVVITLKNMASHPVSLHAVGV (SEQ ID NO:740), wherein the peptide consists of from 9 to 180 amino acids.

[0087] In a specific embodiment, the FVIII peptide has the sequence: $(R^1)_x$-P-$(R^2)_y$, wherein P is an amino acid sequence having at least 85% identity to a sequence of at least nine consecutive

amino acids of a sequence selected from SEQ ID NOS:68, 344, and 740, R1 is an amino acid sequence consisting of from 1 to 80 amino acids; R2 is an amino acid sequence consisting of from 1 to 80 amino acids; and each of x and y are independently zero or one. In one embodiment, R^1 is an amino acid sequence consisting of from 1 to 40 amino acids, and R^2 is an amino acid sequence consisting of from 1 to 40 amino acids.

[0088] In one embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 80 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 70 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 60 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 50 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 40 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 30 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 20 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 10 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 5 amino acids. In yet other embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, or 80 amino acids.

[0089] In one embodiment, the FVIII peptide consists of from 9 to 150 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 100 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 50 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 25 amino acids. In yet other embodiments, the FVIII peptide consists of from 9 to 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, or 180 amino acids.

[0090] Generally, the FVIII peptides of the present invention can include any sequence of amino acids present in the identified region of $FVIII^{102-122}$, $FVIII^{246-266}$, or $FVIII^{1401-1424}$,or a modified variant that can, for example, have a retained function similar or identical to $FVIII^{102-122}$, $FVIII^{246-266}$, or $FVIII^{1401-1424}$. In particular, the FVIII peptides of the present invention include a sequence of amino acids that includes a T cell epitope. The FVIII peptides include a sequence of at least nine amino acids that can range in percent identity relative to the amino acid sequence AWPKMHTVNGYVNRSLPGLIG (SEQ ID NO:68); QANRSPLPIAKVSSFPSIRPIYLT (SEQ ID NO:344); or TVVITLKNMASHPVSLHAVGV (SEQ ID NO:740). For example, a FVIII peptides can have nine amino acids that are identical or at least 50%, 60%, 70%, 80%, or 85% percent identical to any of nine consecutive amino acids in $FVIII^{102-122}$, $FVIII^{246-266}$, or $FVIII^{1401-1424}$.

[0091] In another group of embodiments, the FVIII peptides can have amino acid sequences greater than nine amino acids, in which the amino acid sequences include a region that can be identical or at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% percent identical to the sequence of consecutive amino acids in $FVIII^{102-122}$, $FVIII^{246-266}$, or $FVIII^{1401-1424}$. One of ordinary skill in the art will appreciate that known mutagenesis techniques, such as alanine substitution, can be used to identify modified variants that retain the function of the $FVIII^{102-122}$, $FVIII^{246-266}$, or $FVIII^{1401-1424}$ region.

[0092] In addition, the FVIII peptides can further include additional sequences of amino acids on either end of the core sequence of the FVIII peptides discussed above. The additional sequences are designated $(R^1)_x$ and $(R^2)_y$. In certain embodiments, R^1 and R^2 can range from 1 to about 80 amino acids in length. Alternatively, R^1 and R^2 can range from 1 to about 40 amino acids in length. In certain embodiments, each of the subscripts x and y are independently zero or one. In some embodiments, both x and y can be zero. In other embodiments, x can be one and y can be zero. In yet other embodiments, x can be zero and y can be one. In another embodiment, both x and y are one. Additional amino acids on either end can be added for a variety of reasons, including increased stability of the peptides, improved binding to MHC class II molecules and/or T cells, as well as other aspects that will be appreciated by one of ordinary skill in the art.

[0093] In one embodiment, the present invention provides a polypeptide having the sequence $(R^1)_x$-P-$(R^2)_y$, wherein P is an amino acid sequence having at least 85% identity to a sequence of at least nine consecutive amino acids of a Factor VIII region identified in Table 1, R^1 is an amino

acid sequence consisting of from 1 to 80 amino acids, and R^2 is an amino acid sequence consisting of from 1 to 80 amino acids, wherein each of x and y are independently zero or one. Alternatively, R^1 and R^2 can range from 1 to about 40 amino acids in length. In one embodiment, P is an amino acid sequence having at least 90% identity to a sequence of at least nine consecutive amino acids of a Factor VIII region identified in Table 1. In another embodiment, P is an amino acid sequence having at least 95% identity to a sequence of at least nine consecutive amino acids of a Factor VIII region identified in Table 1. In some embodiments, both x and y can be zero. In other embodiments, x can be one and y can be zero. In other embodiments, x can be zero and y can be one. In yet another embodiment, both x and y can be one. In one embodiment, the FVIII peptide consists of from 9 to 150 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 100 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 50 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 25 amino acids.

Table 1. Regions of FVIII including T-cell epitopes

Regions including T cell epitopes	Amino Acid Sequence
$FVIII^{102-119}$	TVVITLKNMASHPVSLHA (SEQ ID NO:10)
$FVIII^{246-266}$	AWPKMHTVNGYVNRSLPGLIG (SEQ ID NO:68)
$FVIII^{474-494}$	GEVGDTLLIIFKNQASRPYNI (SEQ ID NO:159)
$FVIII^{540-560}$	PTKSDPRCLTRYYSSFVNMER (SEQ ID NO:250)
$FVIII^{1401-1424}$	QANRSPLPIAKVSSFPSIRPIYLT (SEQ ID NO:344)
$FVIII^{1785-1805}$	EVEDNIMVTFRNQASRPYSFY (SEQ ID NO:477)
$FVIII^{2025-2045}$	LHAGMSTLFLVYSNKCQTPLG (SEQ ID NO:568)
$FVIII^{2160-2180}$	NPPIIARYIRLHPTHYSIRST (SEQ ID NO:659)
$FVIII^{102-122}$	TVVITLKNMASHPVSLHAVGV (SEQ ID NO:740)

[0094] As described above, the FVIII peptides of the present invention can include any sequence of amino acids present in the identified region of $FVIII^{1401-1424}$ or a modified variant that can, for example, have a retained function similar or identical to $FVIII^{1401-1424}$. In certain embodiments, the peptides can cover the whole B-domain of human FVIII protein. The present invention also can include other FVIII peptides that include a peptide having a sequence of at least nine amino acids that can range in percent identity relative to any one of the following

amino acid sequences: GEVGDTLLIIFKNQASRPYNI ($FVIII^{474-494}$; SEQ ID NO:159), PTKSDPRCLTRYYSSFVNMER ($FVIII^{540-560}$; SEQ ID NO:250), EVEDNIMVTFRNQASRPYSFY ($FVIII^{1785-1805}$; SEQ ID NO:477), LHAGMSTLFLVYSNKCQTPLG ($FVIII^{2025-2045}$; SEQ ID NO:568), NPPIIARYIRLHPTHYSIRST ($FVIII^{2160-2180}$; SEQ ID NO:659), TVVITLKNMASHPVSLHA ($FVIII^{102-119}$; SEQ ID NO:10), AWPKMHTVNGYVNRSLPGLIG ($FVIII^{246-266}$; SEQ ID NO:68), and TVVITLKNMASHPVSLHAVGV ($FVIII^{102-122}$; SEQ ID NO:740).

[0095] For example, the FVIII peptides having nine amino acids that are identical or at least 50%, 60%, 70%, 80%, or 85% percent identical to any of nine consecutive amino acids in $FVIII^{474-494}$, $FVIII^{540-560}$, $FVIII^{1785-1805}$, $FVIII^{2025-2045}$, $FVIII^{2160-2180}$, $FVIII^{102-119}$, $FVIII^{246-266}$, or $FVIII^{102-122}$. In another group of embodiments, the FVIII peptides can have amino acid sequences greater than nine amino acids, in which the amino acid sequences can be identical or at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% percent identical to any of nine consecutive amino acids in $FVIII^{474-494}$, $FVIII^{540-560}$, $FVIII^{1785-1805}$, $FVIII^{2025-2045}$, $FVIII^{2160-2180}$, $FVIII^{102-119}$, $FVIII^{246-266}$, or $FVIII^{102-122}$. One of ordinary skill in the art will appreciate that known mutagenesis techniques, such as alanine substitution, can be used to identify modified variants that retain the function of the $FVIII^{474-494}$, $FVIII^{540-560}$, $FVIII^{1785-1805}$, $FVIII^{2025-2045}$, $FVIII^{2160-2180}$, $FVIII^{102-119}$, $FVIII^{246-266}$, or $FVIII^{102-122}$ regions. The FVIII peptides disclosed here can be made using methods described above with respect to the FVIII peptides relating to $FVIII^{1401-1424}$.

A. Factor $VIII^{102-119}$ Peptides

[0096] In one embodiment, the present invention provides a polypeptide having the sequence $(R^1)_x$-P-$(R^2)_y$, wherein P is an amino acid sequence having at least 85% identity to a sequence of at least nine consecutive amino acids of a Factor $VIII^{102-119}$ peptide having the sequence: TVVITLKNMASHPVSLHA (SEQ ID NO:10), R^1 is an amino acid sequence consisting of from 1 to 80 amino acids, and R^2 is an amino acid sequence consisting of from 1 to 80 amino acids, wherein each of x and y are independently zero or one.

[0097] In one embodiment, P is an amino acid sequence having at least 90% identity to a sequence of at least nine consecutive amino acids of a Factor $VIII^{102-119}$ peptide having the sequence: TVVITLKNMASHPVSLHA (SEQ ID NO:10). In one embodiment, P is an amino

acid sequence having at least 85% identity to a sequence selected from SEQ ID NOS:1 to 55 (SEQ ID NO:10). In one embodiment, P is an amino acid sequence having at least 90% identity to a sequence selected from SEQ ID NOS:1 to 55. In one embodiment, P is an amino acid sequence selected from SEQ ID NOS:1 to 55. In some embodiments, both x and y can be zero. In other embodiments, x can be one and y can be zero. In other embodiments, x can be zero and y can be one. In yet another embodiment, both x and y can be one.

[0098] In one embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 80 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 70 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 60 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 50 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 40 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 30 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 20 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 10 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 5 amino acids. In yet other embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, or 80 amino acids.

[0099] In certain embodiments, R^1 is an amino acid sequence consisting of from 1 to 40 amino acids, and R^2 is an amino acid sequence consisting of from 1 to 40 amino acids. In one embodiment, the FVIII peptide consists of from 9 to 150 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 100 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 50 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 25 amino acids. In yet other embodiments, the FVIII peptide consists of from 9 to 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87,

88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, or 180 amino acids.

Table 2. Exemplary FVIII$^{102-119}$ Peptides

Peptide	Sequence	SEQ ID NO:
FVIII$^{102-119}$-1	TVVITLKNM	1
FVIII$^{102-119}$-2	TVVITLKNMA	2
FVIII$^{102-119}$-3	TVVITLKNMAS	3
FVIII$^{102-119}$-4	TVVITLKNMASH	4
FVIII$^{102-119}$-5	TVVITLKNMASHP	5
FVIII$^{102-119}$-6	TVVITLKNMASHPV	6
FVIII$^{102-119}$-7	TVVITLKNMASHPVS	7
FVIII$^{102-119}$-8	TVVITLKNMASHPVSL	8
FVIII$^{102-119}$-9	TVVITLKNMASHPVSLH	9
FVIII$^{102-119}$-10	TVVITLKNMASHPVSLHA	10
FVIII$^{102-119}$-11	VVITLKNMA	11
FVIII$^{102-119}$-12	VVITLKNMAS	12
FVIII$^{102-119}$-13	VVITLKNMASH	13
FVIII$^{102-119}$-14	VVITLKNMASHP	14
FVIII$^{102-119}$-15	VVITLKNMASHPV	15
FVIII$^{102-119}$-16	VVITLKNMASHPVS	16
FVIII$^{102-119}$-17	VVITLKNMASHPVSL	17
FVIII$^{102-119}$-18	VVITLKNMASHPVSLH	18
FVIII$^{102-119}$-19	VVITLKNMASHPVSLHA	19
FVIII$^{102-119}$-20	VITLKNMAS	20
FVIII$^{102-119}$-21	VITLKNMASH	21
FVIII$^{102-119}$-22	VITLKNMASHP	22
FVIII$^{102-119}$-23	VITLKNMASHPV	23
FVIII$^{102-119}$-24	VITLKNMASHPVS	24
FVIII$^{102-119}$-25	VITLKNMASHPVSL	25
FVIII$^{102-119}$-26	VITLKNMASHPVSLH	26
FVIII$^{102-119}$-27	VITLKNMASHPVSLHA	27
FVIII$^{102-119}$-28	ITLKNMASH	28
FVIII$^{102-119}$-29	ITLKNMASHP	29
FVIII$^{102-119}$-30	ITLKNMASHPV	30
FVIII$^{102-119}$-31	ITLKNMASHPVS	31
FVIII$^{102-119}$-32	ITLKNMASHPVSL	32
FVIII$^{102-119}$-33	ITLKNMASHPVSLH	33
FVIII$^{102-119}$-34	ITLKNMASHPVSLHA	34
FVIII$^{102-119}$-35	TLKNMASHP	35
FVIII$^{102-119}$-36	TLKNMASHPV	36
FVIII$^{102-119}$-37	TLKNMASHPVS	37
FVIII$^{102-119}$-38	TLKNMASHPVSL	38
FVIII$^{102-119}$-39	TLKNMASHPVSLH	39
FVIII$^{102-119}$-40	TLKNMASHPVSLHA	40
FVIII$^{102-119}$-41	LKNMASHPV	41
FVIII$^{102-119}$-42	LKNMASHPVS	42
FVIII$^{102-119}$-43	LKNMASHPVSL	43

$FVIII^{102-119}$-44	LKNMASHPVSLH	44
$FVIII^{102-119}$-45	LKNMASHPVSLHA	45
$FVIII^{102-119}$-46	KNMASHPVS	46
$FVIII^{102-119}$-47	KNMASHPVSL	47
$FVIII^{102-119}$-48	KNMASHPVSLH	48
$FVIII^{102-119}$-49	KNMASHPVSLHA	49
$FVIII^{102-119}$-50	NMASHPVSL	50
$FVIII^{102-119}$-51	NMASHPVSLH	51
$FVIII^{102-119}$-52	NMASHPVSLHA	52
$FVIII^{102-119}$-53	MASHPVSLH	53
$FVIII^{102-119}$-54	MASHPVSLHA	54
$FVIII^{102-119}$-55	ASHPVSLHA	55

B. Factor $VIII^{246-266}$ Peptides

[0100] In one embodiment, the present invention provides a polypeptide having the sequence $(R^1)_x$-P-$(R^2)_y$, wherein P is an amino acid sequence having at least 85% identity to a sequence of at least nine consecutive amino acids of a Factor $VIII^{246-266}$ peptide having the sequence: AWPKMHTVNGYVNRSLPGLIG (SEQ ID NO:68), R^1 is an amino acid sequence consisting of from 1 to 80 amino acids, and R^2 is an amino acid sequence consisting of from 1 to 80 amino acids, wherein each of x and y are independently zero or one.

[0101] In one embodiment, P is an amino acid sequence having at least 90% identity to a sequence of at least nine consecutive amino acids of a Factor $VIII^{246-266}$ peptide having the sequence: AWPKMHTVNGYVNRSLPGLIG (SEQ ID NO:68). In one embodiment, P is an amino acid sequence having at least 95% identity to a sequence of at least nine consecutive amino acids of a Factor $VIII^{246-266}$ peptide having the sequence: AWPKMHTVNGYVNRSLPGLIG (SEQ ID NO:68). In one embodiment, P is an amino acid sequence having at least 85% identity to a sequence selected from SEQ ID NOS:56 to 146. In one embodiment, P is an amino acid sequence having at least 90% identity to a sequence selected from SEQ ID NOS:56 to 146. In one embodiment, P is an amino acid sequence having at least 95% identity to a sequence selected from SEQ ID NOS:56 to 146. In one embodiment, P is an amino acid sequence selected from SEQ ID NOS:56 to 146. In some embodiments, both x and y can be zero. In other embodiments, x can be one and y can be zero. In other embodiments, x can be zero and y can be one. In yet another embodiment, both x and y can be one.

[0102] In one embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 80 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 70 amino acids. In another embodiment, R^1 and R^2 are

seperately or both amino acid sequences consisting of from 1 to 60 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 50 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 40 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 30 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 20 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 10 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 5 amino acids. In yet other embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, or 80 amino acids.

[0103] In one embodiment, the FVIII peptide consists of from 9 to 150 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 100 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 50 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 25 amino acids. In yet other embodiments, the FVIII peptide consists of from 9 to 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, or 180 amino acids.

Table 3. Exemplary $FVIII^{246-266}$ Peptides

Peptide	Sequence	SEQ ID NO:
$FVIII^{246-266}$-1	AWPKMHTVN	56
$FVIII^{246-266}$-2	AWPKMHTVNG	57
$FVIII^{246-266}$-3	AWPKMHTVNGY	58
$FVIII^{246-266}$-4	AWPKMHTVNGYV	59
$FVIII^{246-266}$-5	AWPKMHTVNGYVN	60
$FVIII^{246-266}$-6	AWPKMHTVNGYVNR	61
$FVIII^{246-266}$-7	AWPKMHTVNGYVNRS	62
$FVIII^{246-266}$-8	AWPKMHTVNGYVNRSL	63
$FVIII^{246-266}$-9	AWPKMHTVNGYVNRSLP	64
$FVIII^{246-266}$-10	AWPKMHTVNGYVNRSLPG	65
$FVIII^{246-266}$-11	AWPKMHTVNGYVNRSLPGL	66
$FVIII^{246-266}$-12	AWPKMHTVNGYVNRSLPGLI	67

$FVIII^{246-266}$-13	AWPKMHTVNGYVNRSLPGLIG	68
$FVIII^{246-266}$-14	WPKMHTVNG	69
$FVIII^{246-266}$-15	WPKMHTVNGY	70
$FVIII^{246-266}$-16	WPKMHTVNGYV	71
$FVIII^{246-266}$-17	WPKMHTVNGYVN	72
$FVIII^{246-266}$-18	WPKMHTVNGYVNR	73
$FVIII^{246-266}$-19	WPKMHTVNGYVNRS	74
$FVIII^{246-266}$-20	WPKMHTVNGYVNRSL	75
$FVIII^{246-266}$-21	WPKMHTVNGYVNRSLP	76
$FVIII^{246-266}$-22	WPKMHTVNGYVNRSLPG	77
$FVIII^{246-266}$-23	WPKMHTVNGYVNRSLPGL	78
$FVIII^{246-266}$-24	WPKMHTVNGYVNRSLPGLI	79
$FVIII^{246-266}$-25	WPKMHTVNGYVNRSLPGLIG	80
$FVIII^{246-266}$-26	PKMHTVNGY	81
$FVIII^{246-266}$-27	PKMHTVNGYV	82
$FVIII^{246-266}$-28	PKMHTVNGYVN	83
$FVIII^{246-266}$-29	PKMHTVNGYVNR	84
$FVIII^{246-266}$-30	PKMHTVNGYVNRS	85
$FVIII^{246-266}$-31	PKMHTVNGYVNRSL	86
$FVIII^{246-266}$-32	PKMHTVNGYVNRSLP	87
$FVIII^{246-266}$-33	PKMHTVNGYVNRSLPG	88
$FVIII^{246-266}$-34	PKMHTVNGYVNRSLPGL	89
$FVIII^{246-266}$-35	PKMHTVNGYVNRSLPGLI	90
$FVIII^{246-266}$-36	PKMHTVNGYVNRSLPGLIG	91
$FVIII^{246-266}$-37	KMHTVNGYV	92
$FVIII^{246-266}$-38	KMHTVNGYVN	93
$FVIII^{246-266}$-39	KMHTVNGYVNR	94
$FVIII^{246-266}$-40	KMHTVNGYVNRS	95
$FVIII^{246-266}$-41	KMHTVNGYVNRSL	96
$FVIII^{246-266}$-42	KMHTVNGYVNRSLP	97
$FVIII^{246-266}$-43	KMHTVNGYVNRSLPG	98
$FVIII^{246-266}$-44	KMHTVNGYVNRSLPGL	99
$FVIII^{246-266}$-45	KMHTVNGYVNRSLPGLI	100
$FVIII^{246-266}$-46	KMHTVNGYVNRSLPGLIG	101
$FVIII^{246-266}$-47	MHTVNGYVN	102
$FVIII^{246-266}$-48	MHTVNGYVNR	103
$FVIII^{246-266}$-49	MHTVNGYVNRS	104
$FVIII^{246-266}$-50	MHTVNGYVNRSL	105
$FVIII^{246-266}$-51	MHTVNGYVNRSLP	106
$FVIII^{246-266}$-52	MHTVNGYVNRSLPG	107
$FVIII^{246-266}$-53	MHTVNGYVNRSLPGL	108
$FVIII^{246-266}$-54	MHTVNGYVNRSLPGLI	109
$FVIII^{246-266}$-55	MHTVNGYVNRSLPGLIG	110
$FVIII^{246-266}$-56	HTVNGYVNR	111
$FVIII^{246-266}$-57	HTVNGYVNRS	112
$FVIII^{246-266}$-58	HTVNGYVNRSL	113
$FVIII^{246-266}$-59	HTVNGYVNRSLP	114
$FVIII^{246-266}$-60	HTVNGYVNRSLPG	115
$FVIII^{246-266}$-61	HTVNGYVNRSLPGL	116

$FVIII^{246-266}$-62	HTVNGYVNRSLPGLI	117
$FVIII^{246-266}$-63	HTVNGYVNRSLPGLIG	118
$FVIII^{246-266}$-64	TVNGYVNRS	119
$FVIII^{246-266}$-65	TVNGYVNRSL	120
$FVIII^{246-266}$-66	TVNGYVNRSLP	121
$FVIII^{246-266}$-67	TVNGYVNRSLPG	122
$FVIII^{246-266}$-68	TVNGYVNRSLPGL	123
$FVIII^{246-266}$-69	TVNGYVNRSLPGLI	124
$FVIII^{246-266}$-70	TVNGYVNRSLPGLIG	125
$FVIII^{246-266}$-71	VNGYVNRSL	126
$FVIII^{246-266}$-72	VNGYVNRSLP	127
$FVIII^{246-266}$-73	VNGYVNRSLPG	128
$FVIII^{246-266}$-74	VNGYVNRSLPGL	129
$FVIII^{246-266}$-75	VNGYVNRSLPGLI	130
$FVIII^{246-266}$-76	VNGYVNRSLPGLIG	131
$FVIII^{246-266}$-77	NGYVNRSLP	132
$FVIII^{246-266}$-78	NGYVNRSLPG	133
$FVIII^{246-266}$-79	NGYVNRSLPGL	134
$FVIII^{246-266}$-80	NGYVNRSLPGLI	135
$FVIII^{246-266}$-81	NGYVNRSLPGLIG	136
$FVIII^{246-266}$-82	GYVNRSLPG	137
$FVIII^{246-266}$-83	GYVNRSLPGL	138
$FVIII^{246-266}$-84	GYVNRSLPGLI	139
$FVIII^{246-266}$-85	GYVNRSLPGLIG	140
$FVIII^{246-266}$-86	YVNRSLPGL	141
$FVIII^{246-266}$-87	YVNRSLPGLI	142
$FVIII^{246-266}$-88	YVNRSLPGLIG	143
$FVIII^{246-266}$-89	VNRSLPGLI	144
$FVIII^{246-266}$-90	VNRSLPGLIG	145
$FVIII^{246-266}$-91	NRSLPGLIG	146

C. Factor $VIII^{474-494}$ Peptides

[0104] In one embodiment, the present invention provides a polypeptide having the sequence $(R^1)_x$-P-$(R^2)_y$, wherein P is an amino acid sequence having at least 85% identity to a sequence of at least nine consecutive amino acids of a Factor $VIII^{474-494}$ peptide having the sequence: GEVGDTLLIIFKNQASRPYNI (SEQ ID NO:159), R^1 is an amino acid sequence consisting of from 1 to 80 amino acids, and R^2 is an amino acid sequence consisting of from 1 to 80 amino acids, wherein each of x and y are independently zero or one.

[0105] In one embodiment, P is an amino acid sequence having at least 90% identity to a sequence of at least nine consecutive amino acids of a Factor $VIII^{474-494}$ peptide having the sequence: GEVGDTLLIIFKNQASRPYNI (SEQ ID NO:159). In one embodiment, P is an amino acid sequence having at least 95% identity to a sequence of at least nine consecutive

amino acids of a Factor $VIII^{474-494}$ peptide having the sequence: GEVGDTLLIIFKNQASRPYNI (SEQ ID NO:159). In one embodiment, P is an amino acid sequence having at least 85% identity to a sequence selected from SEQ ID NOS:147 to 237. In one embodiment, P is an amino acid sequence having at least 90% identity to a sequence selected from SEQ ID NOS:147 to 237. In one embodiment, P is an amino acid sequence having at least 95% identity to a sequence selected from SEQ ID NOS:147 to 237. In one embodiment, P is an amino acid sequence selected from SEQ ID NOS:147 to 237. In some embodiments, both x and y can be zero. In other embodiments, x can be one and y can be zero. In other embodiments, x can be zero and y can be one. In yet another embodiment, both x and y can be one.

[0106] In certain embodiments, R^1 is an amino acid sequence consisting of from 1 to 40 amino acids, and R^2 is an amino acid sequence consisting of from 1 to 40 amino acids. In one embodiment, the FVIII peptide consists of from 9 to 150 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 100 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 50 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 25 amino acids. In yet other embodiments, the FVIII peptide consists of from 9 to 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, or 180 amino acids.

Table 4. Exemplary $FVIII^{474-494}$ Peptides

Peptide	Sequence	SEQ ID NO:
$FVIII^{474-494}$-1	GEVGDTLLI	147
$FVIII^{474-494}$-2	GEVGDTLLII	148
$FVIII^{474-494}$-3	GEVGDTLLIIF	149
$FVIII^{474-494}$-4	GEVGDTLLIIFK	150
$FVIII^{474-494}$-5	GEVGDTLLIIFKN	151
$FVIII^{474-494}$-6	GEVGDTLLIIFKNQ	152
$FVIII^{474-494}$-7	GEVGDTLLIIFKNQA	153
$FVIII^{474-494}$-8	GEVGDTLLIIFKNQAS	154
$FVIII^{474-494}$-9	GEVGDTLLIIFKNQASR	155
$FVIII^{474-494}$-10	GEVGDTLLIIFKNQASRP	156
$FVIII^{474-494}$-11	GEVGDTLLIIFKNQASRPY	157
$FVIII^{474-494}$-12	GEVGDTLLIIFKNQASRPYN	158
$FVIII^{474-494}$-13	GEVGDTLLIIFKNQASRPYNI	159
$FVIII^{474-494}$-14	EVGDTLLII	160
$FVIII^{474-494}$-15	EVGDTLLIIF	161

FVIII$^{474-494}$-16	EVGDTLLIIFK	162
FVIII$^{474-494}$-17	EVGDTLLIIFKN	163
FVIII$^{474-494}$-18	EVGDTLLIIFKNQ	164
FVIII$^{474-494}$-19	EVGDTLLIIFKNQA	165
FVIII$^{474-494}$-20	EVGDTLLIIFKNQAS	166
FVIII$^{474-494}$-21	EVGDTLLIIFKNQASR	167
FVIII$^{474-494}$-22	EVGDTLLIIFKNQASRP	168
FVIII$^{474-494}$-23	EVGDTLLIIFKNQASRPY	169
FVIII$^{474-494}$-24	EVGDTLLIIFKNQASRPYN	170
FVIII$^{474-494}$-25	EVGDTLLIIFKNQASRPYNI	171
FVIII$^{474-494}$-26	VGDTLLIIF	172
FVIII$^{474-494}$-27	VGDTLLIIFK	173
FVIII$^{474-494}$-28	VGDTLLIIFKN	174
FVIII$^{474-494}$-29	VGDTLLIIFKNQ	175
FVIII$^{474-494}$-30	VGDTLLIIFKNQA	176
FVIII$^{474-494}$-31	VGDTLLIIFKNQAS	177
FVIII$^{474-494}$-32	VGDTLLIIFKNQASR	178
FVIII$^{474-494}$-33	VGDTLLIIFKNQASRP	179
FVIII$^{474-494}$-34	VGDTLLIIFKNQASRPY	180
FVIII$^{474-494}$-35	VGDTLLIIFKNQASRPYN	181
FVIII$^{474-494}$-36	VGDTLLIIFKNQASRPYNI	182
FVIII$^{474-494}$-37	GDTLLIIFK	183
FVIII$^{474-494}$-38	GDTLLIIFKN	184
FVIII$^{474-494}$-39	GDTLLIIFKNQ	185
FVIII$^{474-494}$-40	GDTLLIIFKNQA	186
FVIII$^{474-494}$-41	GDTLLIIFKNQAS	187
FVIII$^{474-494}$-42	GDTLLIIFKNQASR	188
FVIII$^{474-494}$-43	GDTLLIIFKNQASRP	189
FVIII$^{474-494}$-44	GDTLLIIFKNQASRPY	190
FVIII$^{474-494}$-45	GDTLLIIFKNQASRPYN	191
FVIII$^{474-494}$-46	GDTLLIIFKNQASRPYNI	192
FVIII$^{474-494}$-47	DTLLIIFKN	193
FVIII$^{474-494}$-48	DTLLIIFKNQ	194
FVIII$^{474-494}$-49	DTLLIIFKNQA	195
FVIII$^{474-494}$-50	DTLLIIFKNQAS	196
FVIII$^{474-494}$-51	DTLLIIFKNQASR	197
FVIII$^{474-494}$-52	DTLLIIFKNQASRP	198
FVIII$^{474-494}$-53	DTLLIIFKNQASRPY	199
FVIII$^{474-494}$-54	DTLLIIFKNQASRPYN	200
FVIII$^{474-494}$-55	DTLLIIFKNQASRPYNI	201
FVIII$^{474-494}$-56	TLLIIFKNQ	202
FVIII$^{474-494}$-57	TLLIIFKNQA	203
FVIII$^{474-494}$-58	TLLIIFKNQAS	204
FVIII$^{474-494}$-59	TLLIIFKNQASR	205
FVIII$^{474-494}$-60	TLLIIFKNQASRP	206
FVIII$^{474-494}$-61	TLLIIFKNQASRPY	207
FVIII$^{474-494}$-62	TLLIIFKNQASRPYN	208
FVIII$^{474-494}$-63	TLLIIFKNQASRPYNI	209
FVIII$^{474-494}$-64	LLIIFKNQA	210
FVIII$^{474-494}$-65	LLIIFKNQAS	211

$FVIII^{474-494}$-66	LLIIFKNQASR	212
$FVIII^{474-494}$-67	LLIIFKNQASRP	213
$FVIII^{474-494}$-68	LLIIFKNQASRPY	214
$FVIII^{474-494}$-69	LLIIFKNQASRPYN	215
$FVIII^{474-494}$-70	LLIIFKNQASRPYNI	216
$FVIII^{474-494}$-71	LIIFKNQAS	217
$FVIII^{474-494}$-72	LIIFKNQASR	218
$FVIII^{474-494}$-73	LIIFKNQASRP	219
$FVIII^{474-494}$-74	LIIFKNQASRPY	220
$FVIII^{474-494}$-75	LIIFKNQASRPYN	221
$FVIII^{474-494}$-76	LIIFKNQASRPYNI	222
$FVIII^{474-494}$-77	IIFKNQASR	223
$FVIII^{474-494}$-78	IIFKNQASRP	224
$FVIII^{474-494}$-79	IIFKNQASRPY	225
$FVIII^{474-494}$-80	IIFKNQASRPYN	226
$FVIII^{474-494}$-81	IIFKNQASRPYNI	227
$FVIII^{474-494}$-82	IFKNQASRP	228
$FVIII^{474-494}$-83	IFKNQASRPY	229
$FVIII^{474-494}$-84	IFKNQASRPYN	230
$FVIII^{474-494}$-85	IFKNQASRPYNI	231
$FVIII^{474-494}$-86	FKNQASRPY	232
$FVIII^{474-494}$-87	FKNQASRPYN	233
$FVIII^{474-494}$-88	FKNQASRPYNI	234
$FVIII^{474-494}$-89	KNQASRPYN	235
$FVIII^{474-494}$-90	KNQASRPYNI	236
$FVIII^{474-494}$-91	NQASRPYNI	237

D. Factor $VIII^{540-560}$ Peptides

[0107] In one embodiment, the present invention provides a polypeptide having the sequence $(R^1)_x$-P-$(R^2)_y$, wherein P is an amino acid sequence having at least 85% identity to a sequence of at least nine consecutive amino acids of a Factor $VIII^{540-560}$ peptide having the sequence: PTKSDPRCLTRYYSSFVNMER (SEQ ID NO:250), R^1 is an amino acid sequence consisting of from 1 to 80 amino acids, and R^2 is an amino acid sequence consisting of from 1 to 80 amino acids, wherein each of x and y are independently zero or one.

[0108] In one embodiment, P is an amino acid sequence having at least 90% identity to a sequence of at least nine consecutive amino acids of a Factor $VIII^{540-560}$ peptide having the sequence: PTKSDPRCLTRYYSSFVNMER (SEQ ID NO:250). In one embodiment, P is an amino acid sequence having at least 95% identity to a sequence of at least nine consecutive amino acids of a Factor $VIII^{540-560}$ peptide having the sequence: PTKSDPRCLTRYYSSFVNMER (SEQ ID NO:250). In one embodiment, P is an amino acid sequence having at least 85% identity to a sequence selected from SEQ ID NOS:238 to 328. In

one embodiment, P is an amino acid sequence having at least 90% identity to a sequence selected from SEQ ID NOS:238 to 328. In one embodiment, P is an amino acid sequence having at least 95% identity to a sequence selected from SEQ ID NOS:238 to 328. In one embodiment, P is an amino acid sequence selected from SEQ ID NOS:238 to 328. In some embodiments, both x and y can be zero. In other embodiments, x can be one and y can be zero. In other embodiments, x can be zero and y can be one. In yet another embodiment, both x and y can be one.

[0109] In one embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 80 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 70 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 60 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 50 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 40 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 30 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 20 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 10 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 5 amino acids. In yet other embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, or 80 amino acids.

[0110] In one embodiment, the FVIII peptide consists of from 9 to 150 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 100 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 50 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 25 amino acids. In yet other embodiments, the FVIII peptide consists of from 9 to 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, or 180 amino acids.

Table 5. Exemplary FVIII$^{540-560}$ Peptides

Peptide	Sequence	SEQ ID NO:
FVIII$^{540-560}$-1	PTKSDPRCL	238
FVIII$^{540-560}$-2	PTKSDPRCLT	239
FVIII$^{540-560}$-3	PTKSDPRCLTR	240
FVIII$^{540-560}$-4	PTKSDPRCLTRY	241
FVIII$^{540-560}$-5	PTKSDPRCLTRYY	242
FVIII$^{540-560}$-6	PTKSDPRCLTRYYS	243
FVIII$^{540-560}$-7	PTKSDPRCLTRYYSS	244
FVIII$^{540-560}$-8	PTKSDPRCLTRYYSSF	245
FVIII$^{540-560}$-9	PTKSDPRCLTRYYSSFV	246
FVIII$^{540-560}$-10	PTKSDPRCLTRYYSSFVN	247
FVIII$^{540-560}$-11	PTKSDPRCLTRYYSSFVNM	248
FVIII$^{540-560}$-12	PTKSDPRCLTRYYSSFVNME	249
FVIII$^{540-560}$-13	PTKSDPRCLTRYYSSFVNMER	250
FVIII$^{540-560}$-14	TKSDPRCLT	251
FVIII$^{540-560}$-15	TKSDPRCLTR	252
FVIII$^{540-560}$-16	TKSDPRCLTRY	253
FVIII$^{540-560}$-17	TKSDPRCLTRYY	254
FVIII$^{540-560}$-18	TKSDPRCLTRYYS	255
FVIII$^{540-560}$-19	TKSDPRCLTRYYSS	256
FVIII$^{540-560}$-20	TKSDPRCLTRYYSSF	257
FVIII$^{540-560}$-21	TKSDPRCLTRYYSSFV	258
FVIII$^{540-560}$-22	TKSDPRCLTRYYSSFVN	259
FVIII$^{540-560}$-23	TKSDPRCLTRYYSSFVNM	260
FVIII$^{540-560}$-24	TKSDPRCLTRYYSSFVNME	261
FVIII$^{540-560}$-25	TKSDPRCLTRYYSSFVNMER	262
FVIII$^{540-560}$-26	KSDPRCLTR	263
FVIII$^{540-560}$-27	KSDPRCLTRY	264
FVIII$^{540-560}$-28	KSDPRCLTRYY	265
FVIII$^{540-560}$-29	KSDPRCLTRYYS	266
FVIII$^{540-560}$-30	KSDPRCLTRYYSS	267
FVIII$^{540-560}$-31	KSDPRCLTRYYSSF	268
FVIII$^{540-560}$-32	KSDPRCLTRYYSSFV	269
FVIII$^{540-560}$-33	KSDPRCLTRYYSSFVN	270
FVIII$^{540-560}$-34	KSDPRCLTRYYSSFVNM	271
FVIII$^{540-560}$-35	KSDPRCLTRYYSSFVNME	272
FVIII$^{540-560}$-36	KSDPRCLTRYYSSFVNMER	273
FVIII$^{540-560}$-37	SDPRCLTRY	274
FVIII$^{540-560}$-38	SDPRCLTRYY	275
FVIII$^{540-560}$-39	SDPRCLTRYYS	276
FVIII$^{540-560}$-40	SDPRCLTRYYSS	277
FVIII$^{540-560}$-41	SDPRCLTRYYSSF	278
FVIII$^{540-560}$-42	SDPRCLTRYYSSFV	279
FVIII$^{540-560}$-43	SDPRCLTRYYSSFVN	280
FVIII$^{540-560}$-44	SDPRCLTRYYSSFVNM	281
FVIII$^{540-560}$-45	SDPRCLTRYYSSFVNME	282
FVIII$^{540-560}$-46	SDPRCLTRYYSSFVNMER	283
FVIII$^{540-560}$-47	DPRCLTRYY	284

$FVIII^{540-560}$-48	DPRCLTRYYS	285
$FVIII^{540-560}$-49	DPRCLTRYYSS	286
$FVIII^{540-560}$-50	DPRCLTRYYSSF	287
$FVIII^{540-560}$-51	DPRCLTRYYSSFV	288
$FVIII^{540-560}$-52	DPRCLTRYYSSFVN	289
$FVIII^{540-560}$-53	DPRCLTRYYSSFVNM	290
$FVIII^{540-560}$-54	DPRCLTRYYSSFVNME	291
$FVIII^{540-560}$-55	DPRCLTRYYSSFVNMER	292
$FVIII^{540-560}$-56	PRCLTRYYS	293
$FVIII^{540-560}$-57	PRCLTRYYSS	294
$FVIII^{540-560}$-58	PRCLTRYYSSF	295
$FVIII^{540-560}$-59	PRCLTRYYSSFV	296
$FVIII^{540-560}$-60	PRCLTRYYSSFVN	297
$FVIII^{540-560}$-61	PRCLTRYYSSFVNM	298
$FVIII^{540-560}$-62	PRCLTRYYSSFVNME	299
$FVIII^{540-560}$-63	PRCLTRYYSSFVNMER	300
$FVIII^{540-560}$-64	RCLTRYYSS	301
$FVIII^{540-560}$-65	RCLTRYYSSF	302
$FVIII^{540-560}$-66	RCLTRYYSSFV	303
$FVIII^{540-560}$-67	RCLTRYYSSFVN	304
$FVIII^{540-560}$-68	RCLTRYYSSFVNM	305
$FVIII^{540-560}$-69	RCLTRYYSSFVNME	306
$FVIII^{540-560}$-70	RCLTRYYSSFVNMER	307
$FVIII^{540-560}$-71	CLTRYYSSF	308
$FVIII^{540-560}$-72	CLTRYYSSFV	309
$FVIII^{540-560}$-73	CLTRYYSSFVN	310
$FVIII^{540-560}$-74	CLTRYYSSFVNM	311
$FVIII^{540-560}$-75	CLTRYYSSFVNME	312
$FVIII^{540-560}$-76	CLTRYYSSFVNMER	313
$FVIII^{540-560}$-77	LTRYYSSFV	314
$FVIII^{540-560}$-78	LTRYYSSFVN	315
$FVIII^{540-560}$-79	LTRYYSSFVNM	316
$FVIII^{540-560}$-80	LTRYYSSFVNME	317
$FVIII^{540-560}$-81	LTRYYSSFVNMER	318
$FVIII^{540-560}$-82	TRYYSSFVN	319
$FVIII^{540-560}$-83	TRYYSSFVNM	320
$FVIII^{540-560}$-84	TRYYSSFVNME	321
$FVIII^{540-560}$-85	TRYYSSFVNMER	322
$FVIII^{540-560}$-86	RYYSSFVNM	323
$FVIII^{540-560}$-87	RYYSSFVNME	324
$FVIII^{540-560}$-88	RYYSSFVNMER	325
$FVIII^{540-560}$-89	YYSSFVNME	326
$FVIII^{540-560}$-90	YYSSFVNMER	327
$FVIII^{540-560}$-91	YSSFVNMER	328

E. Factor $VIII^{1401-1424}$ Peptides

[0111] In one embodiment, the present invention provides a polypeptide having the sequence $(R^1)_x$-P-$(R^2)_y$, wherein P is an amino acid sequence having at least 85% identity to a sequence of

at least nine consecutive amino acids of a Factor $VIII^{1401-1424}$ peptide having the sequence: QANRSPLPIAKVSSFPSIRPIYLT (SEQ ID NO:344), R^1 is an amino acid sequence consisting of from 1 to 80 amino acids, and R^2 is an amino acid sequence consisting of from 1 to 80 amino acids, wherein each of x and y are independently zero or one.

[0112] In one embodiment, P is an amino acid sequence having at least 90% identity to a sequence of at least nine consecutive amino acids of a Factor $VIII^{1401-1424}$ peptide having the sequence: QANRSPLPIAKVSSFPSIRPIYLT (SEQ ID NO:344). In one embodiment, P is an amino acid sequence having at least 95% identity to a sequence of at least nine consecutive amino acids of a Factor $VIII^{1401-1424}$ peptide having the sequence: QANRSPLPIAKVSSFPSIRPIYLT (SEQ ID NO:344). In one embodiment, P is an amino acid sequence having at least 85% identity to a sequence selected from SEQ ID NOS:329 to 464. In one embodiment, P is an amino acid sequence having at least 90% identity to a sequence selected from SEQ ID NOS:329 to 464. In one embodiment, P is an amino acid sequence having at least 95% identity to a sequence selected from SEQ ID NOS:329 to 464. In one embodiment, P is an amino acid sequence selected from SEQ ID NOS:329 to 464. In some embodiments, both x and y can be zero. In other embodiments, x can be one and y can be zero. In other embodiments, x can be zero and y can be one. In yet another embodiment, both x and y can be one.

[0113] In one embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 80 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 70 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 60 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 50 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 40 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 30 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 20 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 10 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 5 amino acids. In yet other embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43,

44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, or 80 amino acids.

[0114] In one embodiment, the FVIII peptide consists of from 9 to 150 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 100 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 50 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 25 amino acids. In yet other embodiments, the FVIII peptide consists of from 9 to 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, or 180 amino acids.

Table 6. Exemplary $FVIII^{1401-1424}$ Peptides

Peptide	Sequence	SEQ ID NO:
$FVIII^{1401-1424}$-1	QANRSPLPI	329
$FVIII^{1401-1424}$-2	QANRSPLPIA	330
$FVIII^{1401-1424}$-3	QANRSPLPIAK	331
$FVIII^{1401-1424}$-4	QANRSPLPIAKV	332
$FVIII^{1401-1424}$-5	QANRSPLPIAKVS	333
$FVIII^{1401-1424}$-6	QANRSPLPIAKVSS	334
$FVIII^{1401-1424}$-7	QANRSPLPIAKVSSF	335
$FVIII^{1401-1424}$-8	QANRSPLPIAKVSSFP	336
$FVIII^{1401-1424}$-9	QANRSPLPIAKVSSFPS	337
$FVIII^{1401-1424}$-10	QANRSPLPIAKVSSFPSI	338
$FVIII^{1401-1424}$-11	QANRSPLPIAKVSSFPSIR	339
$FVIII^{1401-1424}$-12	QANRSPLPIAKVSSFPSIRP	340
$FVIII^{1401-1424}$-13	QANRSPLPIAKVSSFPSIRPI	341
$FVIII^{1401-1424}$-14	QANRSPLPIAKVSSFPSIRPIY	342
$FVIII^{1401-1424}$-15	QANRSPLPIAKVSSFPSIRPIYL	343
$FVIII^{1401-1424}$-16	QANRSPLPIAKVSSFPSIRPIYLT	344
$FVIII^{1401-1424}$-17	ANRSPLPIA	345
$FVIII^{1401-1424}$-18	ANRSPLPIAK	346
$FVIII^{1401-1424}$-19	ANRSPLPIAKV	347
$FVIII^{1401-1424}$-20	ANRSPLPIAKVS	348
$FVIII^{1401-1424}$-21	ANRSPLPIAKVSS	349
$FVIII^{1401-1424}$-22	ANRSPLPIAKVSSF	350
$FVIII^{1401-1424}$-23	ANRSPLPIAKVSSFP	351
$FVIII^{1401-1424}$-24	ANRSPLPIAKVSSFPS	352
$FVIII^{1401-1424}$-25	ANRSPLPIAKVSSFPSI	353
$FVIII^{1401-1424}$-26	ANRSPLPIAKVSSFPSIR	354
$FVIII^{1401-1424}$-27	ANRSPLPIAKVSSFPSIRP	355
$FVIII^{1401-1424}$-28	ANRSPLPIAKVSSFPSIRPI	356
$FVIII^{1401-1424}$-29	ANRSPLPIAKVSSFPSIRPIY	357

$FVIII^{1401-1424}$-30	ANRSPLPIAKVSSFPSIRPIYL	358
$FVIII^{1401-1424}$-31	ANRSPLPIAKVSSFPSIRPIYLT	359
$FVIII^{1401-1424}$-32	NRSPLPIAK	360
$FVIII^{1401-1424}$-33	NRSPLPIAKV	361
$FVIII^{1401-1424}$-34	NRSPLPIAKVS	362
$FVIII^{1401-1424}$-35	NRSPLPIAKVSS	363
$FVIII^{1401-1424}$-36	NRSPLPIAKVSSF	364
$FVIII^{1401-1424}$-37	NRSPLPIAKVSSFP	365
$FVIII^{1401-1424}$-38	NRSPLPIAKVSSFPS	366
$FVIII^{1401-1424}$-39	NRSPLPIAKVSSFPSI	367
$FVIII^{1401-1424}$-40	NRSPLPIAKVSSFPSIR	368
$FVIII^{1401-1424}$-41	NRSPLPIAKVSSFPSIRP	369
$FVIII^{1401-1424}$-42	NRSPLPIAKVSSFPSIRPI	370
$FVIII^{1401-1424}$-43	NRSPLPIAKVSSFPSIRPIY	371
$FVIII^{1401-1424}$-44	NRSPLPIAKVSSFPSIRPIYL	372
$FVIII^{1401-1424}$-45	NRSPLPIAKVSSFPSIRPIYLT	373
$FVIII^{1401-1424}$-46	RSPLPIAKV	374
$FVIII^{1401-1424}$-47	RSPLPIAKVS	375
$FVIII^{1401-1424}$-48	RSPLPIAKVSS	376
$FVIII^{1401-1424}$-49	RSPLPIAKVSSF	377
$FVIII^{1401-1424}$-50	RSPLPIAKVSSFP	378
$FVIII^{1401-1424}$-51	RSPLPIAKVSSFPS	379
$FVIII^{1401-1424}$-52	RSPLPIAKVSSFPSI	380
$FVIII^{1401-1424}$-53	RSPLPIAKVSSFPSIR	381
$FVIII^{1401-1424}$-54	RSPLPIAKVSSFPSIRP	382
$FVIII^{1401-1424}$-55	RSPLPIAKVSSFPSIRPI	383
$FVIII^{1401-1424}$-56	RSPLPIAKVSSFPSIRPIY	384
$FVIII^{1401-1424}$-57	RSPLPIAKVSSFPSIRPIYL	385
$FVIII^{1401-1424}$-58	RSPLPIAKVSSFPSIRPIYLT	386
$FVIII^{1401-1424}$-59	SPLPIAKVS	387
$FVIII^{1401-1424}$-60	SPLPIAKVSS	388
$FVIII^{1401-1424}$-61	SPLPIAKVSSF	389
$FVIII^{1401-1424}$-62	SPLPIAKVSSFP	390
$FVIII^{1401-1424}$-63	SPLPIAKVSSFPS	391
$FVIII^{1401-1424}$-64	SPLPIAKVSSFPSI	392
$FVIII^{1401-1424}$-65	SPLPIAKVSSFPSIR	393
$FVIII^{1401-1424}$-66	SPLPIAKVSSFPSIRP	394
$FVIII^{1401-1424}$-67	SPLPIAKVSSFPSIRPI	395
$FVIII^{1401-1424}$-68	SPLPIAKVSSFPSIRPIY	396
$FVIII^{1401-1424}$-69	SPLPIAKVSSFPSIRPIYL	397
$FVIII^{1401-1424}$-70	SPLPIAKVSSFPSIRPIYLT	398
$FVIII^{1401-1424}$-71	PLPIAKVSS	399
$FVIII^{1401-1424}$-72	PLPIAKVSSF	400
$FVIII^{1401-1424}$-73	PLPIAKVSSFP	401
$FVIII^{1401-1424}$-74	PLPIAKVSSFPS	402
$FVIII^{1401-1424}$-75	PLPIAKVSSFPSI	403
$FVIII^{1401-1424}$-76	PLPIAKVSSFPSIR	404
$FVIII^{1401-1424}$-77	PLPIAKVSSFPSIRP	405
$FVIII^{1401-1424}$-78	PLPIAKVSSFPSIRPI	406
$FVIII^{1401-1424}$-79	PLPIAKVSSFPSIRPIY	407

FVIII$^{1401-1424}$-80	PLPIAKVSSFPSIRPIYL	408
FVIII$^{1401-1424}$-81	PLPIAKVSSFPSIRPIYLT	409
FVIII$^{1401-1424}$-82	LPIAKVSSF	410
FVIII$^{1401-1424}$-83	LPIAKVSSFP	411
FVIII$^{1401-1424}$-84	LPIAKVSSFPS	412
FVIII$^{1401-1424}$-85	LPIAKVSSFPSI	413
FVIII$^{1401-1424}$-86	LPIAKVSSFPSIR	414
FVIII$^{1401-1424}$-87	LPIAKVSSFPSIRP	415
FVIII$^{1401-1424}$-88	LPIAKVSSFPSIRPI	416
FVIII$^{1401-1424}$-89	LPIAKVSSFPSIRPIY	417
FVIII$^{1401-1424}$-90	LPIAKVSSFPSIRPIYL	418
FVIII$^{1401-1424}$-91	LPIAKVSSFPSIRPIYLT	419
FVIII$^{1401-1424}$-92	PIAKVSSFP	420
FVIII$^{1401-1424}$-93	PIAKVSSFPS	421
FVIII$^{1401-1424}$-94	PIAKVSSFPSI	422
FVIII$^{1401-1424}$-95	PIAKVSSFPSIR	423
FVIII$^{1401-1424}$-96	PIAKVSSFPSIRP	424
FVIII$^{1401-1424}$-97	PIAKVSSFPSIRPI	425
FVIII$^{1401-1424}$-98	PIAKVSSFPSIRPIY	426
FVIII$^{1401-1424}$-99	PIAKVSSFPSIRPIYL	427
FVIII$^{1401-1424}$-100	PIAKVSSFPSIRPIYLT	428
FVIII$^{1401-1424}$-101	IAKVSSFPS	429
FVIII$^{1401-1424}$-102	IAKVSSFPSI	430
FVIII$^{1401-1424}$-103	IAKVSSFPSIR	431
FVIII$^{1401-1424}$-104	IAKVSSFPSIRP	432
FVIII$^{1401-1424}$-105	IAKVSSFPSIRPI	433
FVIII$^{1401-1424}$-106	IAKVSSFPSIRPIY	434
FVIII$^{1401-1424}$-107	IAKVSSFPSIRPIYL	435
FVIII$^{1401-1424}$-108	IAKVSSFPSIRPIYLT	436
FVIII$^{1401-1424}$-109	AKVSSFPSI	437
FVIII$^{1401-1424}$-110	AKVSSFPSIR	438
FVIII$^{1401-1424}$-111	AKVSSFPSIRP	439
FVIII$^{1401-1424}$-112	AKVSSFPSIRPI	440
FVIII$^{1401-1424}$-113	AKVSSFPSIRPIY	441
FVIII$^{1401-1424}$-114	AKVSSFPSIRPIYL	442
FVIII$^{1401-1424}$-115	AKVSSFPSIRPIYLT	443
FVIII$^{1401-1424}$-116	KVSSFPSIR	444
FVIII$^{1401-1424}$-117	KVSSFPSIRP	445
FVIII$^{1401-1424}$-118	KVSSFPSIRPI	446
FVIII$^{1401-1424}$-119	KVSSFPSIRPIY	447
FVIII$^{1401-1424}$-120	KVSSFPSIRPIYL	448
FVIII$^{1401-1424}$-121	KVSSFPSIRPIYLT	449
FVIII$^{1401-1424}$-122	VSSFPSIRP	450
FVIII$^{1401-1424}$-123	VSSFPSIRPI	451
FVIII$^{1401-1424}$-124	VSSFPSIRPIY	452
FVIII$^{1401-1424}$-125	VSSFPSIRPIYL	453
FVIII$^{1401-1424}$-126	VSSFPSIRPIYLT	454
FVIII$^{1401-1424}$-127	SSFPSIRPI	455
FVIII$^{1401-1424}$-128	SSFPSIRPIY	456
FVIII$^{1401-1424}$-129	SSFPSIRPIYL	457

$FVIII^{1401-1424}$-130	SSFPSIRPIYLT	458
$FVIII^{1401-1424}$-131	SFPSIRPIY	459
$FVIII^{1401-1424}$-132	SFPSIRPIYL	460
$FVIII^{1401-1424}$-133	SFPSIRPIYLT	461
$FVIII^{1401-1424}$-134	FPSIRPIYL	462
$FVIII^{1401-1424}$-135	FPSIRPIYLT	463
$FVIII^{1401-1424}$-136	PSIRPIYLT	464

F. Factor $VIII^{1785-1805}$ Peptides

[0115] In one embodiment, the present invention provides a polypeptide having the sequence $(R^1)_x$-P-$(R^2)_y$, wherein P is an amino acid sequence having at least 85% identity to a sequence of at least nine consecutive amino acids of a Factor $VIII^{1785-1805}$ peptide having the sequence: EVEDNIMVTFRNQASRPYSFY (SEQ ID NO:477), R^1 is an amino acid sequence consisting of from 1 to 80 amino acids, and R^2 is an amino acid sequence consisting of from 1 to 80 amino acids, wherein each of x and y are independently zero or one. In one embodiment, P is an amino acid sequence having at least 90% identity to a sequence of at least nine consecutive amino acids of a Factor $VIII^{1785-1805}$ peptide having the sequence: EVEDNIMVTFRNQASRPYSFY (SEQ ID NO:477).

[0116] In one embodiment, P is an amino acid sequence having at least 95% identity to a sequence of at least nine consecutive amino acids of a Factor $VIII^{1785-1805}$ peptide having the sequence: EVEDNIMVTFRNQASRPYSFY (SEQ ID NO:477). In one embodiment, P is an amino acid sequence having at least 85% identity to a sequence selected from SEQ ID NOS:465 to 555. In one embodiment, P is an amino acid sequence having at least 90% identity to a sequence selected from SEQ ID NOS:465 to 555. In one embodiment, P is an amino acid sequence having at least 95% identity to a sequence selected from SEQ ID NOS:465 to 555. In one embodiment, P is an amino acid sequence selected from SEQ ID NOS:465 to 555. In some embodiments, both x and y can be zero. In other embodiments, x can be one and y can be zero. In other embodiments, x can be zero and y can be one. In yet another embodiment, both x and y can be one.

[0117] In one embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 80 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 70 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 60 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 50

amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 40 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 30 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 20 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 10 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 5 amino acids. In yet other embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, or 80 amino acids.

[0118] In one embodiment, the FVIII peptide consists of from 9 to 150 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 100 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 50 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 25 amino acids. In yet other embodiments, the FVIII peptide consists of from 9 to 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, or 180 amino acids.

Table 7. Exemplary $FVIII^{1785-1805}$ Peptides

Peptide	Sequence	SEQ ID NO:
$FVIII^{1785-1805}$-1	EVEDNIMVT	465
$FVIII^{1785-1805}$-2	EVEDNIMVTF	466
$FVIII^{1785-1805}$-3	EVEDNIMVTFR	467
$FVIII^{1785-1805}$-4	EVEDNIMVTFRN	468
$FVIII^{1785-1805}$-5	EVEDNIMVTFRNQ	469
$FVIII^{1785-1805}$-6	EVEDNIMVTFRNQA	470
$FVIII^{1785-1805}$-7	EVEDNIMVTFRNQAS	471
$FVIII^{1785-1805}$-8	EVEDNIMVTFRNQASR	472
$FVIII^{1785-1805}$-9	EVEDNIMVTFRNQASRP	473
$FVIII^{1785-1805}$-10	EVEDNIMVTFRNQASRPY	474
$FVIII^{1785-1805}$-11	EVEDNIMVTFRNQASRPYS	475
$FVIII^{1785-1805}$-12	EVEDNIMVTFRNQASRPYSF	476
$FVIII^{1785-1805}$-13	EVEDNIMVTFRNQASRPYSFY	477
$FVIII^{1785-1805}$-14	VEDNIMVTF	478
$FVIII^{1785-1805}$-15	VEDNIMVTFR	479

FVIII$^{1785-1805}$-16	VEDNIMVTFRN	480
FVIII$^{1785-1805}$-17	VEDNIMVTFRNQ	481
FVIII$^{1785-1805}$-18	VEDNIMVTFRNQA	482
FVIII$^{1785-1805}$-19	VEDNIMVTFRNQAS	483
FVIII$^{1785-1805}$-20	VEDNIMVTFRNQASR	484
FVIII$^{1785-1805}$-21	VEDNIMVTFRNQASRP	485
FVIII$^{1785-1805}$-22	VEDNIMVTFRNQASRPY	486
FVIII$^{1785-1805}$-23	VEDNIMVTFRNQASRPYS	487
FVIII$^{1785-1805}$-24	VEDNIMVTFRNQASRPYSF	488
FVIII$^{1785-1805}$-25	VEDNIMVTFRNQASRPYSFY	489
FVIII$^{1785-1805}$-26	EDNIMVTFR	490
FVIII$^{1785-1805}$-27	EDNIMVTFRN	491
FVIII$^{1785-1805}$-28	EDNIMVTFRNQ	492
FVIII$^{1785-1805}$-29	EDNIMVTFRNQA	493
FVIII$^{1785-1805}$-30	EDNIMVTFRNQAS	494
FVIII$^{1785-1805}$-31	EDNIMVTFRNQASR	495
FVIII$^{1785-1805}$-32	EDNIMVTFRNQASRP	496
FVIII$^{1785-1805}$-33	EDNIMVTFRNQASRPY	497
FVIII$^{1785-1805}$-34	EDNIMVTFRNQASRPYS	498
FVIII$^{1785-1805}$-35	EDNIMVTFRNQASRPYSF	499
FVIII$^{1785-1805}$-36	EDNIMVTFRNQASRPYSFY	500
FVIII$^{1785-1805}$-37	DNIMVTFRN	501
FVIII$^{1785-1805}$-38	DNIMVTFRNQ	502
FVIII$^{1785-1805}$-39	DNIMVTFRNQA	503
FVIII$^{1785-1805}$-40	DNIMVTFRNQAS	504
FVIII$^{1785-1805}$-41	DNIMVTFRNQASR	505
FVIII$^{1785-1805}$-42	DNIMVTFRNQASRP	506
FVIII$^{1785-1805}$-43	DNIMVTFRNQASRPY	507
FVIII$^{1785-1805}$-44	DNIMVTFRNQASRPYS	508
FVIII$^{1785-1805}$-45	DNIMVTFRNQASRPYSF	509
FVIII$^{1785-1805}$-46	DNIMVTFRNQASRPYSFY	510
FVIII$^{1785-1805}$-47	NIMVTFRNQ	511
FVIII$^{1785-1805}$-48	NIMVTFRNQA	512
FVIII$^{1785-1805}$-49	NIMVTFRNQAS	513
FVIII$^{1785-1805}$-50	NIMVTFRNQASR	514
FVIII$^{1785-1805}$-51	NIMVTFRNQASRP	515
FVIII$^{1785-1805}$-52	NIMVTFRNQASRPY	516
FVIII$^{1785-1805}$-53	NIMVTFRNQASRPYS	517
FVIII$^{1785-1805}$-54	NIMVTFRNQASRPYSF	518
FVIII$^{1785-1805}$-55	NIMVTFRNQASRPYSFY	519
FVIII$^{1785-1805}$-56	IMVTFRNQA	520
FVIII$^{1785-1805}$-57	IMVTFRNQAS	521
FVIII$^{1785-1805}$-58	IMVTFRNQASR	522
FVIII$^{1785-1805}$-59	IMVTFRNQASRP	523
FVIII$^{1785-1805}$-60	IMVTFRNQASRPY	524
FVIII$^{1785-1805}$-61	IMVTFRNQASRPYS	525
FVIII$^{1785-1805}$-62	IMVTFRNQASRPYSF	526
FVIII$^{1785-1805}$-63	IMVTFRNQASRPYSFY	527
FVIII$^{1785-1805}$-64	MVTFRNQAS	528
FVIII$^{1785-1805}$-65	MVTFRNQASR	529

FVIII$^{1785\text{-}1805}$-66	MVTFRNQASRP	530
FVIII$^{1785\text{-}1805}$-67	MVTFRNQASRPY	531
FVIII$^{1785\text{-}1805}$-68	MVTFRNQASRPYS	532
FVIII$^{1785\text{-}1805}$-69	MVTFRNQASRPYSF	533
FVIII$^{1785\text{-}1805}$-70	MVTFRNQASRPYSFY	534
FVIII$^{1785\text{-}1805}$-71	VTFRNQASR	535
FVIII$^{1785\text{-}1805}$-72	VTFRNQASRP	536
FVIII$^{1785\text{-}1805}$-73	VTFRNQASRPY	537
FVIII$^{1785\text{-}1805}$-74	VTFRNQASRPYS	538
FVIII$^{1785\text{-}1805}$-75	VTFRNQASRPYSF	539
FVIII$^{1785\text{-}1805}$-76	VTFRNQASRPYSFY	540
FVIII$^{1785\text{-}1805}$-77	TFRNQASRP	541
FVIII$^{1785\text{-}1805}$-78	TFRNQASRPY	542
FVIII$^{1785\text{-}1805}$-79	TFRNQASRPYS	543
FVIII$^{1785\text{-}1805}$-80	TFRNQASRPYSF	544
FVIII$^{1785\text{-}1805}$-81	TFRNQASRPYSFY	545
FVIII$^{1785\text{-}1805}$-82	FRNQASRPY	546
FVIII$^{1785\text{-}1805}$-83	FRNQASRPYS	547
FVIII$^{1785\text{-}1805}$-84	FRNQASRPYSF	548
FVIII$^{1785\text{-}1805}$-85	FRNQASRPYSFY	549
FVIII$^{1785\text{-}1805}$-86	RNQASRPYS	550
FVIII$^{1785\text{-}1805}$-87	RNQASRPYSF	551
FVIII$^{1785\text{-}1805}$-88	RNQASRPYSFY	552
FVIII$^{1785\text{-}1805}$-89	NQASRPYSF	553
FVIII$^{1785\text{-}1805}$-90	NQASRPYSFY	554
FVIII$^{1785\text{-}1805}$-91	QASRPYSFY	555

G. Factor VIII$^{2025\text{-}2045}$ Peptides

[0119] In one embodiment, the present invention provides a polypeptide having the sequence $(R^1)_x$-P-$(R^2)_y$, wherein P is an amino acid sequence having at least 85% identity to a sequence of at least nine consecutive amino acids of a Factor VIII$^{2025\text{-}2045}$ peptide having the sequence: LHAGMSTLFLVYSNKCQTPLG (SEQ ID NO:568), R^1 is an amino acid sequence consisting of from 1 to 80 amino acids, and R^2 is an amino acid sequence consisting of from 1 to 80 amino acids, wherein each of x and y are independently zero or one.

[0120] In one embodiment, P is an amino acid sequence having at least 90% identity to a sequence of at least nine consecutive amino acids of a Factor VIII$^{2025\text{-}2045}$ peptide having the sequence: LHAGMSTLFLVYSNKCQTPLG (SEQ ID NO:568). In one embodiment, P is an amino acid sequence having at least 95% identity to a sequence of at least nine consecutive amino acids of a Factor VIII$^{2025\text{-}2045}$ peptide having the sequence: LHAGMSTLFLVYSNKCQTPLG (SEQ ID NO:568). In one embodiment, P is an amino acid sequence having at least 85% identity to a sequence selected from SEQ ID NOS:556 to 646. In

one embodiment, P is an amino acid sequence having at least 90% identity to a sequence selected from SEQ ID NOS:556 to 646. In one embodiment, P is an amino acid sequence having at least 95% identity to a sequence selected from SEQ ID NOS:556 to 646. In one embodiment, P is an amino acid sequence selected from SEQ ID NOS:556 to 646. In some embodiments, both x and y can be zero. In other embodiments, x can be one and y can be zero. In other embodiments, x can be zero and y can be one. In yet another embodiment, both x and y can be one.

[0121] In one embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 80 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 70 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 60 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 50 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 40 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 30 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 20 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 10 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 5 amino acids. In yet other embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, or 80 amino acids.

[0122] In one embodiment, the FVIII peptide consists of from 9 to 150 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 100 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 50 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 25 amino acids. In yet other embodiments, the FVIII peptide consists of from 9 to 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, or 180 amino acids.

Table 8. Exemplary FVIII$^{2025-2045}$ Peptides

Peptide	Sequence	SEQ ID NO:
FVIII$^{2025-2045}$-1	LHAGMSTLF	556
FVIII$^{2025-2045}$-2	LHAGMSTLFL	557
FVIII$^{2025-2045}$-3	LHAGMSTLFLV	558
FVIII$^{2025-2045}$-4	LHAGMSTLFLVY	559
FVIII$^{2025-2045}$-5	LHAGMSTLFLVYS	560
FVIII$^{2025-2045}$-6	LHAGMSTLFLVYSN	561
FVIII$^{2025-2045}$-7	LHAGMSTLFLVYSNK	562
FVIII$^{2025-2045}$-8	LHAGMSTLFLVYSNKC	563
FVIII$^{2025-2045}$-9	LHAGMSTLFLVYSNKCQ	564
FVIII$^{2025-2045}$-10	LHAGMSTLFLVYSNKCQT	565
FVIII$^{2025-2045}$-11	LHAGMSTLFLVYSNKCQTP	566
FVIII$^{2025-2045}$-12	LHAGMSTLFLVYSNKCQTPL	567
FVIII$^{2025-2045}$-13	LHAGMSTLFLVYSNKCQTPLG	568
FVIII$^{2025-2045}$-14	HAGMSTLFL	569
FVIII$^{2025-2045}$-15	HAGMSTLFLV	570
FVIII$^{2025-2045}$-16	HAGMSTLFLVY	571
FVIII$^{2025-2045}$-17	HAGMSTLFLVYS	572
FVIII$^{2025-2045}$-18	HAGMSTLFLVYSN	573
FVIII$^{2025-2045}$-19	HAGMSTLFLVYSNK	574
FVIII$^{2025-2045}$-20	HAGMSTLFLVYSNKC	575
FVIII$^{2025-2045}$-21	HAGMSTLFLVYSNKCQ	576
FVIII$^{2025-2045}$-22	HAGMSTLFLVYSNKCQT	577
FVIII$^{2025-2045}$-23	HAGMSTLFLVYSNKCQTP	578
FVIII$^{2025-2045}$-24	HAGMSTLFLVYSNKCQTPL	579
FVIII$^{2025-2045}$-25	HAGMSTLFLVYSNKCQTPLG	580
FVIII$^{2025-2045}$-26	AGMSTLFLV	581
FVIII$^{2025-2045}$-27	AGMSTLFLVY	582
FVIII$^{2025-2045}$-28	AGMSTLFLVYS	583
FVIII$^{2025-2045}$-29	AGMSTLFLVYSN	584
FVIII$^{2025-2045}$-30	AGMSTLFLVYSNK	585
FVIII$^{2025-2045}$-31	AGMSTLFLVYSNKC	586
FVIII$^{2025-2045}$-32	AGMSTLFLVYSNKCQ	587
FVIII$^{2025-2045}$-33	AGMSTLFLVYSNKCQT	588
FVIII$^{2025-2045}$-34	AGMSTLFLVYSNKCQTP	589
FVIII$^{2025-2045}$-35	AGMSTLFLVYSNKCQTPL	590
FVIII$^{2025-2045}$-36	AGMSTLFLVYSNKCQTPLG	591
FVIII$^{2025-2045}$-37	GMSTLFLVY	592
FVIII$^{2025-2045}$-38	GMSTLFLVYS	593
FVIII$^{2025-2045}$-39	GMSTLFLVYSN	594
FVIII$^{2025-2045}$-40	GMSTLFLVYSNK	595
FVIII$^{2025-2045}$-41	GMSTLFLVYSNKC	596
FVIII$^{2025-2045}$-42	GMSTLFLVYSNKCQ	597
FVIII$^{2025-2045}$-43	GMSTLFLVYSNKCQT	598
FVIII$^{2025-2045}$-44	GMSTLFLVYSNKCQTP	599
FVIII$^{2025-2045}$-45	GMSTLFLVYSNKCQTPL	600
FVIII$^{2025-2045}$-46	GMSTLFLVYSNKCQTPLG	601
FVIII$^{2025-2045}$-47	MSTLFLVYS	602

FVIII$^{2025\text{-}2045}$-48	MSTLFLVYSN	603
FVIII$^{2025\text{-}2045}$-49	MSTLFLVYSNK	604
FVIII$^{2025\text{-}2045}$-50	MSTLFLVYSNKC	605
FVIII$^{2025\text{-}2045}$-51	MSTLFLVYSNKCQ	606
FVIII$^{2025\text{-}2045}$-52	MSTLFLVYSNKCQT	607
FVIII$^{2025\text{-}2045}$-53	MSTLFLVYSNKCQTP	608
FVIII$^{2025\text{-}2045}$-54	MSTLFLVYSNKCQTPL	609
FVIII$^{2025\text{-}2045}$-55	MSTLFLVYSNKCQTPLG	610
FVIII$^{2025\text{-}2045}$-56	STLFLVYSN	611
FVIII$^{2025\text{-}2045}$-57	STLFLVYSNK	612
FVIII$^{2025\text{-}2045}$-58	STLFLVYSNKC	613
FVIII$^{2025\text{-}2045}$-59	STLFLVYSNKCQ	614
FVIII$^{2025\text{-}2045}$-60	STLFLVYSNKCQT	615
FVIII$^{2025\text{-}2045}$-61	STLFLVYSNKCQTP	616
FVIII$^{2025\text{-}2045}$-62	STLFLVYSNKCQTPL	617
FVIII$^{2025\text{-}2045}$-63	STLFLVYSNKCQTPLG	618
FVIII$^{2025\text{-}2045}$-64	TLFLVYSNK	619
FVIII$^{2025\text{-}2045}$-65	TLFLVYSNKC	620
FVIII$^{2025\text{-}2045}$-66	TLFLVYSNKCQ	621
FVIII$^{2025\text{-}2045}$-67	TLFLVYSNKCQT	622
FVIII$^{2025\text{-}2045}$-68	TLFLVYSNKCQTP	623
FVIII$^{2025\text{-}2045}$-69	TLFLVYSNKCQTPL	624
FVIII$^{2025\text{-}2045}$-70	TLFLVYSNKCQTPLG	625
FVIII$^{2025\text{-}2045}$-71	LFLVYSNKC	626
FVIII$^{2025\text{-}2045}$-72	LFLVYSNKCQ	627
FVIII$^{2025\text{-}2045}$-73	LFLVYSNKCQT	628
FVIII$^{2025\text{-}2045}$-74	LFLVYSNKCQTP	629
FVIII$^{2025\text{-}2045}$-75	LFLVYSNKCQTPL	630
FVIII$^{2025\text{-}2045}$-76	LFLVYSNKCQTPLG	631
FVIII$^{2025\text{-}2045}$-77	FLVYSNKCQ	632
FVIII$^{2025\text{-}2045}$-78	FLVYSNKCQT	633
FVIII$^{2025\text{-}2045}$-79	FLVYSNKCQTP	634
FVIII$^{2025\text{-}2045}$-80	FLVYSNKCQTPL	635
FVIII$^{2025\text{-}2045}$-81	FLVYSNKCQTPLG	636
FVIII$^{2025\text{-}2045}$-82	LVYSNKCQT	637
FVIII$^{2025\text{-}2045}$-83	LVYSNKCQTP	638
FVIII$^{2025\text{-}2045}$-84	LVYSNKCQTPL	639
FVIII$^{2025\text{-}2045}$-85	LVYSNKCQTPLG	640
FVIII$^{2025\text{-}2045}$-86	VYSNKCQTP	641
FVIII$^{2025\text{-}2045}$-87	VYSNKCQTPL	642
FVIII$^{2025\text{-}2045}$-88	VYSNKCQTPLG	643
FVIII$^{2025\text{-}2045}$-89	YSNKCQTPL	644
FVIII$^{2025\text{-}2045}$-90	YSNKCQTPLG	645
FVIII$^{2025\text{-}2045}$-91	SNKCQTPLG	646

H. Factor VIII$^{2160\text{-}2180}$ Peptides

[0123] In one embodiment, the present invention provides a polypeptide having the sequence $(R^1)_x$-P-$(R^2)_y$, wherein P is an amino acid sequence having at least 85% identity to a sequence of

at least nine consecutive amino acids of a Factor $VIII^{2160-2180}$ peptide having the sequence: NPPIIARYIRLHPTHYSIRST (SEQ ID NO:659), R^1 is an amino acid sequence consisting of from 1 to 80 amino acids, and R^2 is an amino acid sequence consisting of from 1 to 80 amino acids, wherein each of x and y are independently zero or one.

In one embodiment, P is an amino acid sequence having at least 90% identity to a sequence of at least nine consecutive amino acids of a Factor $VIII^{2160-2180}$ peptide having the sequence: NPPIIARYIRLHPTHYSIRST (SEQ ID NO:659). In one embodiment, P is an amino acid sequence having at least 95% identity to a sequence of at least nine consecutive amino acids of a Factor $VIII^{2160-2180}$ peptide having the sequence: NPPIIARYIRLHPTHYSIRST (SEQ ID NO:659). In one embodiment, P is an amino acid sequence having at least 85% identity to a sequence selected from SEQ ID NOS:647 to 737. In one embodiment, P is an amino acid sequence having at least 90% identity to a sequence selected from SEQ ID NOS:647 to 737. In one embodiment, P is an amino acid sequence having at least 95% identity to a sequence selected from SEQ ID NOS:647 to 737. In one embodiment, P is an amino acid sequence selected from SEQ ID NOS:647 to 737. In some embodiments, both x and y can be zero. In other embodiments, x can be one and y can be zero. In other embodiments, x can be zero and y can be one. In yet another embodiment, both x and y can be one.

[0124] In one embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 80 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 70 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 60 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 50 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 40 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 30 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 20 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 10 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 5 amino acids. In yet other embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43,

44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, or 80 amino acids.

[0125] In one embodiment, the FVIII peptide consists of from 9 to 150 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 100 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 50 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 25 amino acids. In yet other embodiments, the FVIII peptide consists of from 9 to 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, or 180 amino acids.

Table 9. Exemplary $FVIII^{2160-2180}$ Peptides

Peptide	Sequence	SEQ ID NO:
$FVIII^{2160-2180}$-1	NPPIIARYI	647
$FVIII^{2160-2180}$-2	NPPIIARYIR	648
$FVIII^{2160-2180}$-3	NPPIIARYIRL	649
$FVIII^{2160-2180}$-4	NPPIIARYIRLH	650
$FVIII^{2160-2180}$-5	NPPIIARYIRLHP	651
$FVIII^{2160-2180}$-6	NPPIIARYIRLHPT	652
$FVIII^{2160-2180}$-7	NPPIIARYIRLHPTH	653
$FVIII^{2160-2180}$-8	NPPIIARYIRLHPTHY	654
$FVIII^{2160-2180}$-9	NPPIIARYIRLHPTHYS	655
$FVIII^{2160-2180}$-10	NPPIIARYIRLHPTHYSI	656
$FVIII^{2160-2180}$-11	NPPIIARYIRLHPTHYSIR	657
$FVIII^{2160-2180}$-12	NPPIIARYIRLHPTHYSIRS	658
$FVIII^{2160-2180}$-13	NPPIIARYIRLHPTHYSIRST	659
$FVIII^{2160-2180}$-14	PPIIARYIR	660
$FVIII^{2160-2180}$-15	PPIIARYIRL	661
$FVIII^{2160-2180}$-16	PPIIARYIRLH	662
$FVIII^{2160-2180}$-17	PPIIARYIRLHP	663
$FVIII^{2160-2180}$-18	PPIIARYIRLHPT	664
$FVIII^{2160-2180}$-19	PPIIARYIRLHPTH	665
$FVIII^{2160-2180}$-20	PPIIARYIRLHPTHY	666
$FVIII^{2160-2180}$-21	PPIIARYIRLHPTHYS	667
$FVIII^{2160-2180}$-22	PPIIARYIRLHPTHYSI	668
$FVIII^{2160-2180}$-23	PPIIARYIRLHPTHYSIR	669
$FVIII^{2160-2180}$-24	PPIIARYIRLHPTHYSIRS	670
$FVIII^{2160-2180}$-25	PPIIARYIRLHPTHYSIRST	671
$FVIII^{2160-2180}$-26	PIIARYIRL	672
$FVIII^{2160-2180}$-27	PIIARYIRLH	673
$FVIII^{2160-2180}$-28	PIIARYIRLHP	674
$FVIII^{2160-2180}$-29	PIIARYIRLHPT	675

$FVIII^{2160-2180}$-30	PIIARYIRLHPTH	676
$FVIII^{2160-2180}$-31	PIIARYIRLHPTHY	677
$FVIII^{2160-2180}$-32	PIIARYIRLHPTHYS	678
$FVIII^{2160-2180}$-33	PIIARYIRLHPTHYSI	679
$FVIII^{2160-2180}$-34	PIIARYIRLHPTHYSIR	680
$FVIII^{2160-2180}$-35	PIIARYIRLHPTHYSIRS	681
$FVIII^{2160-2180}$-36	PIIARYIRLHPTHYSIRST	682
$FVIII^{2160-2180}$-37	IIARYIRLH	683
$FVIII^{2160-2180}$-38	IIARYIRLHP	684
$FVIII^{2160-2180}$-39	IIARYIRLHPT	685
$FVIII^{2160-2180}$-40	IIARYIRLHPTH	686
$FVIII^{2160-2180}$-41	IIARYIRLHPTHY	687
$FVIII^{2160-2180}$-42	IIARYIRLHPTHYS	688
$FVIII^{2160-2180}$-43	IIARYIRLHPTHYSI	689
$FVIII^{2160-2180}$-44	IIARYIRLHPTHYSIR	690
$FVIII^{2160-2180}$-45	IIARYIRLHPTHYSIRS	691
$FVIII^{2160-2180}$-46	IIARYIRLHPTHYSIRST	692
$FVIII^{2160-2180}$-47	IARYIRLHP	693
$FVIII^{2160-2180}$-48	IARYIRLHPT	694
$FVIII^{2160-2180}$-49	IARYIRLHPTH	695
$FVIII^{2160-2180}$-50	IARYIRLHPTHY	696
$FVIII^{2160-2180}$-51	IARYIRLHPTHYS	697
$FVIII^{2160-2180}$-52	IARYIRLHPTHYSI	698
$FVIII^{2160-2180}$-53	IARYIRLHPTHYSIR	699
$FVIII^{2160-2180}$-54	IARYIRLHPTHYSIRS	700
$FVIII^{2160-2180}$-55	IARYIRLHPTHYSIRST	701
$FVIII^{2160-2180}$-56	ARYIRLHPT	702
$FVIII^{2160-2180}$-57	ARYIRLHPTH	703
$FVIII^{2160-2180}$-58	ARYIRLHPTHY	704
$FVIII^{2160-2180}$-59	ARYIRLHPTHYS	705
$FVIII^{2160-2180}$-60	ARYIRLHPTHYSI	706
$FVIII^{2160-2180}$-61	ARYIRLHPTHYSIR	707
$FVIII^{2160-2180}$-62	ARYIRLHPTHYSIRS	708
$FVIII^{2160-2180}$-63	ARYIRLHPTHYSIRST	709
$FVIII^{2160-2180}$-64	RYIRLHPTH	710
$FVIII^{2160-2180}$-65	RYIRLHPTHY	711
$FVIII^{2160-2180}$-66	RYIRLHPTHYS	712
$FVIII^{2160-2180}$-67	RYIRLHPTHYSI	713
$FVIII^{2160-2180}$-68	RYIRLHPTHYSIR	714
$FVIII^{2160-2180}$-69	RYIRLHPTHYSIRS	715
$FVIII^{2160-2180}$-70	RYIRLHPTHYSIRST	716
$FVIII^{2160-2180}$-71	YIRLHPTHY	717
$FVIII^{2160-2180}$-72	YIRLHPTHYS	718
$FVIII^{2160-2180}$-73	YIRLHPTHYSI	719
$FVIII^{2160-2180}$-74	YIRLHPTHYSIR	720
$FVIII^{2160-2180}$-75	YIRLHPTHYSIRS	721
$FVIII^{2160-2180}$-76	YIRLHPTHYSIRST	722
$FVIII^{2160-2180}$-77	IRLHPTHYS	723
$FVIII^{2160-2180}$-78	IRLHPTHYSI	724
$FVIII^{2160-2180}$-79	IRLHPTHYSIR	725

$FVIII^{2160-2180}$-80	IRLHPTHYSIRS	726
$FVIII^{2160-2180}$-81	IRLHPTHYSIRST	727
$FVIII^{2160-2180}$-82	RLHPTHYSI	728
$FVIII^{2160-2180}$-83	RLHPTHYSIR	729
$FVIII^{2160-2180}$-84	RLHPTHYSIRS	730
$FVIII^{2160-2180}$-85	RLHPTHYSIRST	731
$FVIII^{2160-2180}$-86	LHPTHYSIR	732
$FVIII^{2160-2180}$-87	LHPTHYSIRS	733
$FVIII^{2160-2180}$-88	LHPTHYSIRST	734
$FVIII^{2160-2180}$-89	HPTHYSIRS	735
$FVIII^{2160-2180}$-90	HPTHYSIRST	736
$FVIII^{2160-2180}$-91	PTHYSIRST	737

I. Factor $VIII^{102-122}$ Peptides

[0126] In one embodiment, the present invention provides a polypeptide having the sequence $(R^1)_x$-P-$(R^2)_y$, wherein P is an amino acid sequence having at least 85% identity to a sequence of at least nine consecutive amino acids of a Factor $VIII^{102-122}$ peptide having the sequence: TVVITLKNMASHPVSLHAVGV (SEQ ID NO:740), R^1 is an amino acid sequence consisting of from 1 to 80 amino acids, and R^2 is an amino acid sequence consisting of from 1 to 80 amino acids, wherein each of x and y are independently zero or one.

[0127] In one embodiment, P is an amino acid sequence having at least 90% identity to a sequence of at least nine consecutive amino acids of a Factor $VIII^{102-122}$ peptide having the sequence: TVVITLKNMASHPVSLHAVGV (SEQ ID NO:740). In one embodiment, P is an amino acid sequence having at least 95% identity to a sequence of at least nine consecutive amino acids of a Factor $VIII^{102-122}$ peptide having the sequence: TVVITLKNMASHPVSLHAVGV (SEQ ID NO:740).

[0128] In the context of the present invention, $FVIII^{102-122}$ peptides also include $FVIII^{102-119}$ peptides. Accordingly, In one embodiment, P is an amino acid sequence having at least 85% identity to a sequence selected from SEQ ID NOS:1 to 55 and 738 to 773. In one embodiment, P is an amino acid sequence having at least 90% identity to a sequence selected from SEQ ID NOS:1 to 55 and 738 to 773. In one embodiment, P is an amino acid sequence having at least 95% identity to a sequence selected from SEQ ID NOS:1 to 55 and 738 to 773. In one embodiment, P is an amino acid sequence selected from SEQ ID NOS:1 to 55 and 738 to 773. In some embodiments, both x and y can be zero. In other embodiments, x can be one and y can be zero. In other embodiments, x can be zero and y can be one. In yet another embodiment, both x and y can be one.

[0129] In one embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 80 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 70 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 60 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 50 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 40 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 30 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 20 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 10 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 5 amino acids. In yet other embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, or 80 amino acids.

[0130] In one embodiment, the FVIII peptide consists of from 9 to 150 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 100 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 50 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 25 amino acids. In yet other embodiments, the FVIII peptide consists of from 9 to 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, or 180 amino acids.

Table 10. Exemplary $FVIII^{102-122}$ Peptides

Peptide	Sequence	SEQ ID NO:
$FVIII^{102-122}$-738	TVVITLKNMASHPVSLHAV	738
$FVIII^{102-122}$-739	TVVITLKNMASHPVSLHAVG	739
$FVIII^{102-122}$-740	TVVITLKNMASHPVSLHAVGV	740
$FVIII^{102-122}$-741	VVITLKNMASHPVSLHAV	741
$FVIII^{102-122}$-742	VVITLKNMASHPVSLHAVG	742
$FVIII^{102-122}$-743	VVITLKNMASHPVSLHAVGV	743
$FVIII^{102-122}$-744	VITLKNMASHPVSLHAV	744

FVIII$^{102-122}$-745	VITLKNMASHPVSLHAVG	745
FVIII$^{102-122}$-746	VITLKNMASHPVSLHAVGV	746
FVIII$^{102-122}$-747	ITLKNMASHPVSLHAV	747
FVIII$^{102-122}$-748	ITLKNMASHPVSLHAVG	748
FVIII$^{102-122}$-749	ITLKNMASHPVSLHAVGV	749
FVIII$^{102-122}$-750	TLKNMASHPVSLHAV	750
FVIII$^{102-122}$-751	TLKNMASHPVSLHAVG	751
FVIII$^{102-122}$-752	TLKNMASHPVSLHAVGV	752
FVIII$^{102-122}$-753	LKNMASHPVSLHAV	753
FVIII$^{102-122}$-754	LKNMASHPVSLHAVG	754
FVIII$^{102-122}$-755	LKNMASHPVSLHAVGV	755
FVIII$^{102-122}$-756	KNMASHPVSLHAV	756
FVIII$^{102-122}$-757	KNMASHPVSLHAVG	757
FVIII$^{102-122}$-758	KNMASHPVSLHAVGV	758
FVIII$^{102-122}$-759	NMASHPVSLHAV	759
FVIII$^{102-122}$-760	NMASHPVSLHAVG	760
FVIII$^{102-122}$-761	NMASHPVSLHAVGV	761
FVIII$^{102-122}$-762	MASHPVSLHAV	762
FVIII$^{102-122}$-763	MASHPVSLHAVG	763
FVIII$^{102-122}$-764	MASHPVSLHAVGV	764
FVIII$^{102-122}$-765	ASHPVSLHAV	765
FVIII$^{102-122}$-766	ASHPVSLHAVG	766
FVIII$^{102-122}$-767	ASHPVSLHAVGV	767
FVIII$^{102-122}$-768	SHPVSLHAV	768
FVIII$^{102-122}$-769	SHPVSLHAVG	769
FVIII$^{102-122}$-770	SHPVSLHAVGV	770
FVIII$^{102-122}$-771	HPVSLHAVG	771
FVIII$^{102-122}$-772	HPVSLHAVGV	772
FVIII$^{102-122}$-773	PVSLHAVGV	773

IV. Methods of Producing FVIII Peptides

[0131] In another aspect, the present invention further relates to methods for producing FVIII peptides. In some embodiments, the FVIII peptides of the present invention can be produced using solid phase (e.g., Fmoc or *t*-Boc) or liquid phase synthesis techniques generally known in the art. *See, e.g.*, Chan & White, Eds., Fmoc Solid Phase Peptide Synthesis: A Practical Approach (Oxford University Press, 2000); Benoiton, Chemistry of Peptide Synthesis (CRC Press, 2005); Howl, Peptide Synthesis and Applications (Humana Press, 2010).

[0132] In one embodiment, the present invention includes a method of making a FVIII peptide, the method comprising: a) synthesizing a peptide using solid phase or liquid phase synthesis techniques, the FVIII peptide having the sequence: $(R^1)_x$-P-$(R^2)_y$, wherein P is an amino acid sequence having at least 85% identity to a sequence of at least nine consecutive amino acids of a sequence selected from SEQ ID NOS:68, 344, and 740, R1 is an amino acid sequence consisting

of from 1 to 80 amino acids; R2 is an amino acid sequence consisting of from 1 to 80 amino acids; and each of x and y are independently zero or one. In one embodiment, R^1 is an amino acid sequence consisting of from 1 to 40 amino acids, and R^2 is an amino acid sequence consisting of from 1 to 40 amino acids. In certain embodiments, the peptides can cover the whole B-domain of human FVIII protein.

[0133] In one embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 80 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 70 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 60 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 50 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 40 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 30 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 20 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 10 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 5 amino acids. In yet other embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, or 80 amino acids.

[0134] In other embodiments, the peptides can be produced using recombinant techniques. In one embodiment, the present invention includes a method of making a FVIII peptide, the method comprising the steps of: a) providing a culture of cells comprising a vector that encodes a FVIII peptide, the FVIII peptide having the sequence: $(R^1)_x$-P-$(R^2)_y$, wherein P is an amino acid sequence having at least 85% identity to a sequence of at least nine consecutive amino acids of a sequence selected from SEQ ID NOS:68, 344, and 740, R1 is an amino acid sequence consisting of from 1 to 80 amino acids; R2 is an amino acid sequence consisting of from 1 to 80 amino acids; and each of x and y are independently zero or one. In one embodiment, R^1 is an amino acid sequence consisting of from 1 to 40 amino acids, and R^2 is an amino acid sequence consisting of from 1 to 40 amino acids. In certain embodiments, the peptides can cover the whole B-domain of human FVIII protein.

[0135] In one embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 80 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 70 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 60 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 50 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 40 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 30 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 20 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 10 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 5 amino acids. In yet other embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, or 80 amino acids.

[0136] In one embodiment, the present invention provides a method for making a FVIII peptide, the method comprising the steps of: a) providing a culture of cells comprising a polynucleotide that encodes a FVIII peptide, the peptide having the sequence: $(R^1)_x$-P-$(R^2)_y$, wherein P is an amino acid sequence having at least 85% identity to a sequence of at least nine consecutive amino acids of a sequence selected from SEQ ID NOS:10, 68, 159, 250, 344, 477, 568, 659, and 740, R1 is an amino acid sequence consisting of from 1 to 80 amino acids; R2 is an amino acid sequence consisting of from 1 to 80 amino acids; and each of x and y are independently zero or one; and b) expressing the peptide in the culture of cells.

[0137] In one embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 80 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 70 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 60 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 50 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 40 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 30 amino acids. In another embodiment, R^1 and R^2

are seperately or both amino acid sequences consisting of from 1 to 20 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 10 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 5 amino acids. In yet other embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, or 80 amino acids.

[0138] In one embodiment of the methods for producing FVIII peptides, the FVIII peptide consists of from 9 to 150 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 100 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 50 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 25 amino acids. In yet other embodiments, the FVIII peptide consists of from 9 to 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, or 180 amino acids.

[0139] The FVIII peptides of the present invention can be produced by expression in a suitable prokaryotic or eukaryotic host system. Examples of eukaryotic cells include, without limitation, mammalian cells, such as CHO, COS, HEK 293, BHK, SK-Hep, and HepG2; insect cells, for example SF9 cells, SF21 cells, S2 cells, and High Five cells; and yeast cells, for example *Saccharomyces* or *Schizosaccharomyces* cells. In one embodiment, the FVIII peptides can be expressed in bacterial cells, yeast cells, insect cells, avian cells, mammalian cells, and the like. In some embodiments, the peptides can be expressed in a human cell line, a hamster cell line, or a murine cell line. In one particular embodiment, the cell line is a CHO, BHK, or HEK cell line.

[0140] A wide variety of vectors can be used for the expression of the FVIII peptides and can be selected from eukaryotic and prokaryotic expression vectors. The vectors will include a nucleotide sequence necessary for expression of at least one of the FVIII peptides disclosed herein. Examples of vectors for prokaryotic expression include plasmids such as pRSET, pET, pBAD, etc., wherein the promoters used in prokaryotic expression vectors include lac, trc, trp,

recA, araBAD, etc. Examples of vectors for eukaryotic expression include: (i) for expression in yeast, vectors such as pAO, pPIC, pYES, pMET, using promoters such as AOX1, GAP, GAL1, AUG1, etc; (ii) for expression in insect cells, vectors such as pMT, pAc5, pIB, pMIB, pBAC, etc., using promoters such as PH, p10, MT, Ac5, OpIE2, gp64, polh, etc., and (iii) for expression in mammalian cells, vectors such as pSVL, pCMV, pRc/RSV, pcDNA3, pBPV, etc., and vectors derived from viral systems such as vaccinia virus, adeno-associated viruses, herpes viruses, retroviruses, etc., using promoters such as CMV, SV40, EF-1, UbC, RSV, ADV, BPV, and β-actin.

[0141] In some embodiments of the present invention, the nucleic acid sequences for producing the FVIII peptides further include other sequences suitable for a controlled expression of a protein such as promoter sequences, enhancers, TATA boxes, transcription initiation sites, polylinkers, restriction sites, poly-A-sequences, protein processing sequences, selection markers, and the like which are generally known to a person of ordinary skill in the art.

[0142] The culture media used for the cells producing the FVIII peptides can be based on a suitable basal medium well known in the art, e.g., DMEM, Ham's F12, Medium 199, McCoy, or RPMI. The basal medium can include a number of ingredients, including amino acids, vitamins, organic and inorganic salts, and sources of carbohydrate. Each ingredient can be present in an amount that supports the cultivation of a cell, such amounts being generally known to a person skilled in the art. The medium can include auxiliary substances, such as buffer substances, e.g., sodium bicarbonate, antioxidants, stabilizers to counteract mechanical stress, or protease inhibitors. If necessary, a non-ionic surfactant such as copolymers and/or mixtures of polyethylene glycols and polypropylene glycols can be added.

[0143] In some embodiments, the culture medium is free of exogenously added protein. "Protein free" and related terms refers to protein that is from a source exogenous to or other than the cells in the culture, which naturally shed proteins during growth. In another embodiment, the culture medium is polypeptide free. In another embodiment, the culture medium is serum free. In another embodiment the culture medium is animal protein free. In another embodiment the culture medium is animal component free. In another embodiment, the culture medium contains protein, e.g., animal protein from serum such as fetal calf serum. In another embodiment, the culture has recombinant proteins exogenously added. In another embodiment, the proteins are from a certified pathogen free animal.

[0144] Methods of preparing animal protein-free and chemically defined culture mediums are known in the art, for example in US 2008/0009040 and US 2007/0212770, which are both incorporated herein for all purposes. In one embodiment, the culture medium used in the methods described herein is animal protein-free or oligopeptide-free medium. In certain embodiments, the culture medium may be chemically defined. The term "chemically defined" as used herein shall mean, that the medium does not comprise any undefined supplements, such as, for example, extracts of animal components, organs, glands, plants, or yeast. Accordingly, each component of a chemically defined medium is accurately defined.

[0145] In certain embodiments, the methods of the present invention can include the use of a cell-culture system operated in, for example, batch-mode, semi-batch mode, fed-batch mode, or continuous mode. A batch culture can be a large scale cell culture in which a cell inoculum is cultured to a maximum density in a tank or fermenter, and harvested and processed as a batch. A fed-batch culture can be a batch culture which is supplied with either fresh nutrients (e.g., growth-limiting substrates) or additives (e.g., precursors to products). A continuous culture can be a suspension culture that is continuously supplied with nutrients by the inflow of fresh medium, wherein the culture volume is usually constant. Similarly, continuous fermentation can refer to a process in which cells or micro-organisms are maintained in culture in the exponential growth phase by the continuous addition of fresh medium that is exactly balanced by the removal of cell suspension from the bioreactor. Furthermore, the stirred-tank reactor system can be used for suspension, perfusion, chemostatic, and/or microcarrier cultures. Generally, the stirred-tank reactor system can be operated as any conventional stirred-tank reactor with any type of agitator such as a Rushton, hydrofoil, pitched blade, or marine.

[0146] In certain embodiments, the cell-culture methods of the invention can include the use of a microcarrier. In some embodiments, the cell-cultures of the embodiments can be performed in large bioreactors under conditions suitable for providing high volume-specific culture surface areas to achieve high cell densities and protein expression. One means for providing such growth conditions is to use microcarriers for cell-culture in stirred tank bioreactors. The concept of cell-growth on microcarriers was first described by van Wezel (van Wezel, A.L., *Nature* 216:64-5 (1967)) and allows for cell attachment on the surface of small solid particles suspended in the growth medium. These methods provide for high surface-to-volume ratios and thus allow for efficient nutrient utilization. Furthermore, for expression of secreted proteins in eukaryotic cell lines, the increased surface-to-volume ratio allows for higher levels of secretion and thus

higher protein yields in the supernatant of the culture. Finally, these methods allow for the easy scale-up of eukaryotic expression cultures.

[0147] The cells expressing FVIII peptides can be bound to a spherical or a porous microcarrier during cell culture growth. The microcarrier can be a microcarrier selected from the group of microcarriers based on dextran, collagen, plastic, gelatine and cellulose and others. It is also possible to grow the cells to a biomass on spherical microcarriers and subculture the cells when they have reached final fermenter biomass and prior to production of the expressed protein on a porous microcarrier or vice versa. Suitable spherical microcarriers can include smooth surface microcarriers, such as Cytodex™ 1, Cytodex™ 2, and Cytodex™ 3 (GE Healthcare) and macroporous microcarriers such as Cytopore™ 1, Cytopore™ 2, Cytoline™ 1, and Cytoline™ 2 (GE Healthcare).

[0148] One of ordinary skill in the art will appreciate that the FVIII peptides produced by the synthetic and/or recombinant methods described above can include natural and/or non-natural amino acids, including amino acid analogs and/or amino acid mimetics.

V. Factor FVIII Peptide Compositions for Inducing Immune Tolerance

[0149] In another aspect, the FVIII peptides disclosed herein can be included in a pharmaceutical composition. In one embodiment, the present invention provides a pharmaceutical composition comprising a Factor $VIII^{246-266}$ peptide, Factor $VIII^{1401-1424}$ peptide, or Factor $VIII^{102-122}$ peptide, as described herein.

[0150] In one embodiment, the pharmaceutical composition comprises a Factor $VIII^{246-266}$ peptide as described herein. In another embodiment, the pharmaceutical composition further comprises a $FVIII^{474-494}$ peptide, $FVIII^{540-560}$ peptide, $FVIII^{1785-1805}$ peptide, $FVIII^{2025-2045}$ peptide, $FVIII^{2160-2180}$ peptide, $FVIII^{102-119}$ peptide, $FVIII^{1401-1424}$ peptide, $FVIII^{102-122}$ peptide, or second $FVIII^{246-266}$ peptide, as described herein.

[0151] In another embodiment, the pharmaceutical composition comprises a Factor $VIII^{1401-1424}$ peptide as described herein. In another embodiment, the pharmaceutical composition further comprises a $FVIII^{474-494}$ peptide, $FVIII^{540-560}$ peptide, $FVIII^{1785-1805}$ peptide, $FVIII^{2025-2045}$ peptide, $FVIII^{2160-2180}$ peptide, $FVIII^{102-119}$ peptide, $FVIII^{246-266}$ peptide, $FVIII^{102-122}$ peptide, or second $FVIII^{1401-1424}$ peptide, as described herein.

[0152] In another embodiment, the pharmaceutical composition comprises a Factor $VIII^{102-122}$ peptide as described herein. In another embodiment, the pharmaceutical composition further comprises a $FVIII^{474-494}$ peptide, $FVIII^{540-560}$ peptide, $FVIII^{1785-1805}$ peptide, $FVIII^{2025-2045}$ peptide, $FVIII^{2160-2180}$ peptide, $FVIII^{102-119}$ peptide, $FVIII^{246-266}$ peptide, $FVIII^{1401-1424}$ peptide, or second $FVIII^{102-122}$ peptide, as described herein.

[0153] In a specific embodiment, the present invention provides a pharmaceutical composition comprising a peptide having the sequence: $(R^1)_x$-P-$(R^2)_y$, wherein P is an amino acid sequence having at least 85% identity to a sequence of at least nine consecutive amino acids of a sequence selected from SEQ ID NOS:68, 344, and 740, R1 is an amino acid sequence consisting of from 1 to 80 amino acids; R2 is an amino acid sequence consisting of from 1 to 80 amino acids; and each of x and y are independently zero or one. In one embodiment, R^1 is an amino acid sequence consisting of from 1 to 40 amino acids, and R^2 is an amino acid sequence consisting of from 1 to 40 amino acids.

[0154] In one embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 80 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 70 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 60 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 50 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 40 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 30 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 20 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 10 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 5 amino acids. In yet other embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, or 80 amino acids.

[0155] In one embodiment, the FVIII peptide consists of from 9 to 150 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 100 amino acids. In another

embodiment, the FVIII peptide consists of from 9 to 50 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 25 amino acids. In yet other embodiments, the FVIII peptide consists of from 9 to 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, or 180 amino acids.

[0156] In a specific embodiment, the pharmaceutical composition further comprises a second polypeptide, the second polypeptide having the sequence: $(R^1)_x$-P-$(R^2)_y$, wherein P is an amino acid sequence having at least 85% identity to a sequence of at least nine consecutive amino acids of a sequence selected from SEQ ID NOS:10, 68, 159, 250, 344, 477, 568, 659, and 740, R1 is an amino acid sequence consisting of from 1 to 80 amino acids; R2 is an amino acid sequence consisting of from 1 to 80 amino acids; and each of x and y are independently zero or one. In one embodiment, R^1 is an amino acid sequence consisting of from 1 to 40 amino acids, and R^2 is an amino acid sequence consisting of from 1 to 40 amino acids.

[0157] In one embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 80 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 70 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 60 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 50 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 40 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 30 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 20 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 10 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 5 amino acids. In yet other embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, or 80 amino acids.

[0158] In one embodiment, the second FVIII peptide consists of from 9 to 150 amino acids. In another embodiment, the second FVIII peptide consists of from 9 to 100 amino acids. In another embodiment, the second FVIII peptide consists of from 9 to 50 amino acids. In another embodiment, the second FVIII peptide consists of from 9 to 25 amino acids. In yet other embodiments, the second FVIII peptide consists of from 9 to 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, or 180 amino acids.

A. Administration

[0159] To administer compositions to a human or test animal, in one aspect, the compositions can include one or more pharmaceutically acceptable carriers. The phrases "pharmaceutically" or "pharmacologically" acceptable refer to molecular entities and compositions that are stable, inhibit protein or peptide degradation such as aggregation and cleavage products, and in addition do not produce allergic, or other adverse reactions when administered using routes well-known in the art, as described below. "Pharmaceutically acceptable carriers" include any and all clinically useful solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like.

[0160] The pharmaceutical compositions can be administered orally, topically, transdermally, parenterally, by inhalation spray, vaginally, rectally, or by intracranial injection. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intracisternal injection, or infusion techniques. Administration by intravenous, intradermal, intramuscular, intramammary, intraperitoneal, intrathecal, retrobulbar, intrapulmonary injection and or surgical implantation at a particular site is contemplated as well. Generally, compositions are essentially free of pyrogens, as well as other impurities that could be harmful to the recipient.

[0161] Dosages and frequency of administration will depend upon various factors generally appreciated by those of skill in the art, including, e.g., the severity of a patient's hemophilia and/or whether immune tolerance is more effectively induced using larger or smaller doses. Typical daily doses may range from about 0.01 to 100 mg/kg. Doses in the range of 0.07-700 mg FVIII peptide per week may be effective and well tolerated, although even higher weekly

doses may be appropriate and/or well tolerated. The principal determining factor in defining the appropriate dose is the amount of a particular FVIII peptide necessary to be therapeutically effective in a particular context. Repeated administrations may be required in order to achieve longer lasting immune tolerance. Single or multiple administrations of the compositions can be carried out with the dose levels and pattern being selected by the treating physician.

[0162] In one aspect, compositions of the invention can be administered by bolus. As another example, a FVIII peptide can be administered as a one-time dose. Those of ordinary skill in the art will readily optimize effective dosages and administration regimens as determined by good medical practice and the clinical condition of the individual patient. The frequency of dosing depends on the route of administration. The optimal pharmaceutical composition is determined by one skilled in the art depending upon the route of administration and desired dosage. *See e.g.*, Remington: The Science and Practice of Pharmacy (Remington the Science and Practice of Pharmacy), 21st Ed. (2005, Lippincott Williams & Wilkins) the disclosure of which is hereby incorporated by reference. Such compositions influence the physical state, stability, rate of *in vivo* release, and rate of *in vivo* clearance of the administered agents. Depending on the route of administration, a suitable dose is calculated according to body weight, body surface area or organ size. Appropriate dosages may be ascertained through use of established assays for determining blood level dosages in conjunction with appropriate dose-response data. The final dosage regimen is determined by the attending physician, considering various factors which modify the action of drugs, e.g. the drug's specific activity, the severity of the damage and the responsiveness of the patient, the age, condition, body weight, sex and diet of the patient, the severity of any infection, time of administration and other clinical factors.

[0163] In some embodiments, the compositions comprising a FVIII peptide disclosed herein are lyophilized prior to administration. Lyophilization is carried out using techniques common in the art and should be optimized for the composition being developed, as described, e.g., in Tang *et al.*, *Pharm Res.* 21:191-200, (2004) and Chang *et al.*, *Pharm Res.* 13:243-9 (1996). Methods of preparing pharmaceutical compositions can include one or more of the following steps: adding a stabilizing agent to the mixture prior to lyophilizing, adding at least one agent selected from a bulking agent, an osmolarity regulating agent, and a surfactant to the mixture prior to lyophilization. A lyophilized formulation is, in one aspect, at least comprised of one or more of a buffer, a bulking agent, and a stabilizer. In this aspect, the utility of a surfactant is evaluated and selected in cases where aggregation during the lyophilization step or during

reconstitution becomes an issue. An appropriate buffering agent is included to maintain the formulation within stable zones of pH during lyophilization.

[0164] The standard reconstitution practice for lyophilized material is to add back a volume of pure water or sterile water for injection (WFI) (typically equivalent to the volume removed during lyophilization), although dilute solutions of antibacterial agents are sometimes used in the production of pharmaceuticals for parenteral administration. Accordingly, methods are provided for preparation of reconstituted FVIII peptide compositions comprising the step of adding a diluent to a lyophilized FVIII peptide compositions.

[0165] In some embodiments, the lyophilized material may be reconstituted as an aqueous solution. A variety of aqueous carriers, e.g., sterile water for injection, water with preservatives for multi dose use, or water with appropriate amounts of surfactants (for example, an aqueous suspension that contains the active compound in admixture with excipients suitable for the manufacture of aqueous suspensions). In various aspects, such excipients are suspending agents, for example and without limitation, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents are a naturally-occurring phosphatide, for example and without limitation, lecithin, or condensation products of an alkylene oxide with fatty acids, for example and without limitation, polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example and without limitation, heptadecaethyl-eneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example and without limitation, polyethylene sorbitan monooleate. In various aspects, the aqueous suspensions also contain one or more preservatives, for example and without limitation, ethyl, or n-propyl, p-hydroxybenzoate.

VI. Methods of Treatment

[0166] The present invention further relates to methods of treating a patient having a disease associated with the FVIII protein, such as hemophilia A or acquired hemophilia. Such methods can include administration of at least one of the FVIII peptides disclosed herein. In particular, the pharmaceutical compositions including at least one of the FVIII peptides can be administered to induce immune tolerance to FVIII protein in a patient.

[0167] In some embodiments, the methods for inducing an immune tolerance to FVIII can include preventing FVIII inhibitor development after administration of FVIII. The term "preventing" refers to allowing no substantially detectable immune response to FVIII. For example, a patient prior to administration of FVIII protein may not have any detectable anti-FVIII antibodies. However, after administration therapy with FVIII protein the level of detectable anti-FVIII antibodies can increase if a FVIII peptide is not administered to induce immune tolerance. The administration of the FVIII peptides disclosed herein can induce immune tolerance, thereby treating a patient having hemophilia.

[0168] In other embodiments, the methods for inducing an immune tolerance to FVIII protein can include treating patients already having established FVIII inhibitors. In these embodiments, administration of the FVIII peptide can reduce or eliminate the presence of anti-FVIII antibodies. The term "reduce" means a partial reduction in an immune response to FVIII protein. In certain embodiments, reducing the immune response can include a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% reduction in the immune response as compared to the level of the immune response in a patient prior to administration of the FVIII peptide. For example, the percentage reduction can be analyzed by measuring the amount of anti-FVIII antibodies present in the blood prior to and after administration of the FVIII peptide, using standard methods for determining the amount of FVIII antibodies present. In other embodiments, reduction of the immune response can include measuring reduced levels of $CD4^+$ T cells specific for FVIII or FVIII specific B cells secreting FVIII antibodies, or a combination of all three, the T cells, B cells, and the anti-FVIII antibodies. Immune cells, such as T cells and B specific for FVIII can be isolated using methods generally known in the art.

[0169] In one aspect, the present invention includes a method of inducing immune tolerance to FVIII in a subject, the method comprising a step of administering to the subject a therapeutically effective amount of a pharmaceutical composition comprising a FVIII peptide as described herein. In a specific embodiment, the FVIII peptide is a Factor $VIII^{246-266}$ peptide, Factor $VIII^{1401-1424}$ peptide, or Factor $VIII^{102-122}$ peptide, as described herein.

[0170] In one embodiment, the method comprises a step of administering to the subject a therapeutically effective amount of a pharmaceutical composition comprising a Factor $VIII^{246-266}$ peptide as described herein. In another embodiment, the pharmaceutical composition further comprises a $FVIII^{474-494}$ peptide, $FVIII^{540-560}$ peptide, $FVIII^{1785-1805}$ peptide, $FVIII^{2025-2045}$ peptide,

$FVIII^{2160-2180}$ peptide, $FVIII^{102-119}$ peptide, $FVIII^{1401-1424}$ peptide, $FVIII^{102-122}$ peptide, or second $FVIII^{246-266}$ peptide, as described herein.

[0171] In another embodiment, the method comprises a step of administering to the subject a therapeutically effective amount of a pharmaceutical composition comprising a Factor $VIII^{1401-1424}$ peptide as described herein. In another embodiment, the pharmaceutical composition further comprises a $FVIII^{474-494}$ peptide, $FVIII^{540-560}$ peptide, $FVIII^{1785-1805}$ peptide, $FVIII^{2025-2045}$ peptide, $FVIII^{2160-2180}$ peptide, $FVIII^{102-119}$ peptide, $FVIII^{246-266}$ peptide, $FVIII^{102-122}$ peptide, or second $FVIII^{1401-1424}$ peptide, as described herein.

[0172] In another embodiment, the method comprises a step of administering to the subject a therapeutically effective amount of a pharmaceutical composition comprising a Factor $VIII^{102-122}$ peptide as described herein. In another embodiment, the pharmaceutical composition further comprises a $FVIII^{474-494}$ peptide, $FVIII^{540-560}$ peptide, $FVIII^{1785-1805}$ peptide, $FVIII^{2025-2045}$ peptide, $FVIII^{2160-2180}$ peptide, $FVIII^{102-119}$ peptide, $FVIII^{246-266}$ peptide, $FVIII^{1401-1424}$ peptide, or second $FVIII^{102-122}$ peptide, as described herein.

[0173] In one embodiment, the present invention provides a method for inducing an immune tolerance to a FVIII protein, the method comprising administering to the subject a therapeutically effective amount of a pharmaceutical composition comprising a peptide having the sequence: $(R^1)_x$-P-$(R^2)_y$, wherein P is an amino acid sequence having at least 85% identity to a sequence of at least nine consecutive amino acids of a sequence selected from SEQ ID NOS:68, 344, and 740, R1 is an amino acid sequence consisting of from 1 to 80 amino acids; R2 is an amino acid sequence consisting of from 1 to 80 amino acids; and each of x and y are independently zero or one; thereby inducing an immune tolerance to FVIII protein in the subject. In certain embodiments, R^1 is an amino acid sequence consisting of from 1 to 40 amino acids, and R^2 is an amino acid sequence consisting of from 1 to 40 amino acids.

[0174] In one embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 80 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 70 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 60 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 50 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 40 amino acids. In another embodiment, R^1 and R^2 are seperately or both

amino acid sequences consisting of from 1 to 30 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 20 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 10 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 5 amino acids. In yet other embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, or 80 amino acids.

[0175] In one embodiment, the FVIII peptide consists of from 9 to 150 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 100 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 50 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 25 amino acids. In yet other embodiments, the FVIII peptide consists of from 9 to 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, or 180 amino acids.

[0176] The methods of inducing immune tolerance can further include combination therapies in which several peptides can be administered to induce immune tolerance. In one embodiment, the method of inducing immune tolerance further comprises administering a therapeutically effective amount of at least a second peptide having the sequence: $(R^1)_x$-P-$(R^2)_y$, wherein P is an amino acid sequence having at least 85% identity to a sequence of at least nine consecutive amino acids of a sequence selected from SEQ ID NOS:10, 68, 159, 250, 344, 477, 568, 659, and 740, R1 is an amino acid sequence consisting of from 1 to 80 amino acids; R2 is an amino acid sequence consisting of from 1 to 80 amino acids; and each of x and y are independently zero or one; thereby inducing an immune tolerance to FVIII protein in the subject. In certain embodiments, R^1 is an amino acid sequence consisting of from 1 to 40 amino acids, and R^2 is an amino acid sequence consisting of from 1 to 40 amino acids. In a particular embodiment, the second peptide consists of from 9 to 80 amino acids. In another particular embodiment, any additional amino acids in the second peptide are natural amino acids. In another particular embodiment, the second peptide consists of from 9 to 40 amino acids in length. In a specific

embodiment, the second peptide consists of from 9 to 80 amino acids in length and any additional amino acids in the second peptide are natural amino acids.

[0177] In one embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 80 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 70 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 60 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 50 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 40 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 30 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 20 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 10 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 5 amino acids. In yet other embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, or 80 amino acids.

[0178] In one embodiment, the second FVIII peptide consists of from 9 to 150 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 100 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 50 amino acids. In another embodiment, the FVIII peptide consists of from 9 to 25 amino acids. In yet other embodiments, the FVIII peptide consists of from 9 to 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, or 180 amino acids.

[0179] In a specific embodiment of method for inducing an immune tolerance, wherein the administered pharmaceutical composition comprises a peptide where P is an amino acid sequence having at least 85% identity to a sequence of at least nine consecutive amino acids of SEQ ID NO:68, 344, or 740, the composition further comprises a second polypeptide, the second

polypeptide having the sequence: $(R^1)_x$-P-$(R^2)_y$, wherein P is an amino acid sequence having at least 85% identity to a sequence of at least nine consecutive amino acids of a sequence selected from SEQ ID NOS:10, 68, 159, 250, 344, 477, 568, 659, and 740, R1 is an amino acid sequence consisting of from 1 to 80 amino acids; R2 is an amino acid sequence consisting of from 1 to 80 amino acids; and each of x and y are independently zero or one.

[0180] In one embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 80 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 70 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 60 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 50 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 40 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 30 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 20 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 10 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 5 amino acids. In yet other embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, or 80 amino acids.

[0181] In one aspect, the present invention provides the use of a FVIII peptide as described herein for the manufacture of a medicament for the treatment of an immune response generated against FVIII replacement therapy. In a specific embodiment, the FVIII peptide is a $FVIII^{1401-1424}$ peptide. In a related aspect, the present invention provides the use of a FVIII peptide as described herein for the manufacture of a medicament for the prevention of an immune response generated against FVIII replacement therapy. In a specific embodiment, the FVIII peptide is a $FVIII^{1401-1424}$ peptide.

[0182] In one aspect, the present invention provides a FVIII peptide for use as a medicament. In a specific embodiment, the invention provides a polypeptide having the sequence $(R^1)_x$-P-$(R^2)_y$, wherein P is an amino acid sequence having at least 85% identity to a sequence of at least

nine consecutive amino acids of a Factor VIII$^{1401-1424}$ peptide having the sequence: QANRSPLPIAKVSSFPSIRPIYLT (SEQ ID NO:344), R^1 is an amino acid sequence consisting of from 1 to 80 amino acids, and R^2 is an amino acid sequence consisting of from 1 to 80 amino acids, wherein each of x and y are independently zero or one for use as a medicament.

[0183] In one aspect, the present invention provides a FVIII peptide for the treatment of an immune response generated against FVIII replacement therapy. In a specific embodiment, the invention provides a polypeptide having the sequence $(R^1)_x$-P-$(R^2)_y$, wherein P is an amino acid sequence having at least 85% identity to a sequence of at least nine consecutive amino acids of a Factor VIII$^{1401-1424}$ peptide having the sequence: QANRSPLPIAKVSSFPSIRPIYLT (SEQ ID NO:344), R^1 is an amino acid sequence consisting of from 1 to 80 amino acids, and R^2 is an amino acid sequence consisting of from 1 to 80 amino acids, wherein each of x and y are independently zero or one for the treatment of an immune response generated against FVIII replacement therapy.

[0184] In one aspect, the present invention provides a FVIII peptide for the prevention of an immune response generated against FVIII replacement therapy. In a specific embodiment, the invention provides a polypeptide having the sequence $(R^1)_x$-P-$(R^2)_y$, wherein P is an amino acid sequence having at least 85% identity to a sequence of at least nine consecutive amino acids of a Factor VIII$^{1401-1424}$ peptide having the sequence: QANRSPLPIAKVSSFPSIRPIYLT (SEQ ID NO:344), R^1 is an amino acid sequence consisting of from 1 to 80 amino acids, and R^2 is an amino acid sequence consisting of from 1 to 80 amino acids, wherein each of x and y are independently zero or one for the prevention of an immune response generated against FVIII replacement therapy.

VII. Immunodiagnostics

[0185] In one aspect, the present invention provides a method for monitoring FVIII replacement therapy or FVIII immune tolerance induction therapy in a subject in need thereof by identifying the presence or level of a FVIII inhibitory antibody or CD4+ T cell that is specific for FVIII in a biological sample taken from the subject.

[0186] In one embodiment, the method comprises a method for monitoring FVIII replacement therapy in a subject in need thereof, the method comprising: contacting a biological sample from the subject with a FVIII$^{246-266}$ peptide, FVIII$^{1401-1424}$ peptide, or FVIII$^{102-122}$ peptide, as described

herein; and detecting a complex formed between the FVIII peptide and a FVIII inhibitory antibody present in the sample. In one embodiment, the method comprises determining the level of FVIII inhibitory antibody in the sample. In yet another embodiment, the method comprises determining the level of a FVIII inhibitory antibody in at least two samples taken from the subject at different times, and comparing the levels of FVIII inhibitory antibody between the two samples, wherein an increase in the level of antibody over time is indicative of the formation of an immune response against FVIII administered to the subject during the course of the FVIII replacement therapy.

[0187] In another embodiment, the method comprises a method for monitoring FVIII immune tolerance induction therapy in a subject in need thereof, the method comprising: contacting a biological sample from the subject with a $FVIII^{246-266}$ peptide, $FVIII^{1401-1424}$ peptide, or $FVIII^{102-122}$ peptide, as described herein; and detecting a complex formed between the FVIII peptide and a FVIII inhibitory antibody present in the sample. In one embodiment, the method comprises determining the level of FVIII inhibitory antibody in the sample. In yet another embodiment, the method comprises determining the level of a FVIII inhibitory antibody in at least two samples taken from the subject at different times, and comparing the levels of FVIII inhibitory antibody between the two samples, wherein an decrease in the level of antibody over time is indicative of the formation of immune tolerance to FVIII protein in the subject.

[0188] In one embodiment, the method comprises a method for monitoring FVIII replacement therapy in a subject in need thereof, the method comprising: contacting a biological sample from the subject with a $FVIII^{246-266}$ peptide, $FVIII^{1401-1424}$ peptide, or $FVIII^{102-122}$ peptide, as described herein; and detecting a complex formed between the FVIII peptide and a CD4+ T cell specific for FVIII present in the sample. In one embodiment, the method comprises determining the level of CD4+ T cell specific for FVIII in the sample. In yet another embodiment, the method comprises determining the level of a CD4+ T cell specific for FVIII in at least two samples taken from the subject at different times, and comparing the levels of CD4+ T cell specific for FVIII between the two samples, wherein an increase in the level of antibody over time is indicative of the formation of an immune response against FVIII administered to the subject during the course of the FVIII replacement therapy. In a specific embodiment, the FVIII peptide is complexed with a MHC class II multimer.

[0189] In another embodiment, the method comprises a method for monitoring FVIII immune tolerance induction therapy in a subject in need thereof, the method comprising: contacting a biological sample from the subject with a $FVIII^{246-266}$ peptide, $FVIII^{1401-1424}$ peptide, or $FVIII^{102-122}$ peptide, as described herein; and detecting a complex formed between the FVIII peptide and a CD4+ T cell specific for FVIII present in the sample. In one embodiment, the method comprises determining the level of CD4+ T cell specific for FVIII in the sample. In yet another embodiment, the method comprises determining the level of a CD4+ T cell specific for FVIII in at least two samples taken from the subject at different times, and comparing the levels of CD4+ T cell specific for FVIII between the two samples, wherein an decrease in the level of antibody over time is indicative of the formation of immune tolerance to FVIII protein in the subject. In a specific embodiment, the FVIII peptide is complexed with a MHC class II multimer.

[0190] As will be appreciated by one of ordinary skill in the art, immune monitoring can be used, for example, to facilitate treatment of patients with hemophilia. For example, immune monitoring can be used to identify whether administration of the peptides and/or compositions of the present invention is preventing or reducing an immune response to a FVIII product. Dosage amounts and/or dosage intervals can be optimized by immune monitoring. In some embodiments, administration dosages can be tailored specifically based on results from immune monitoring of prevention or reduction of anti-FVIII antibodies. In addition, dosing intervals as well as dosage amounts can be determined for a particular patient or group of patients.

A. Methods of Identifying FVIII-Specific T Cells

[0191] In another aspect, the present invention includes methods of identifying antigen-specific T cells, more specifically T cells that are specific for FVIII protein and the FVIII peptides described herein. Such methods can, for example, be used for immunodiagnostics, such as immune monitoring of a patient. In one embodiment, the present invention includes a method of identifying FVIII peptide-specific T cells, the method comprising a) combining a plurality of $CD4^+$ T cells with a FVIII peptide complexed with a MHC class II multimer, the FVIII peptide having the sequence: $(R^1)_x$-P-$(R^2)_y$, wherein P is an amino acid sequence having at least 85% identity to a sequence of at least nine consecutive amino acids of a sequence selected from SEQ ID NOS:68, 344, and 740, R1 is an amino acid sequence consisting of from 1 to 80 amino acids; R2 is an amino acid sequence consisting of from 1 to 80 amino acids; and each of x and y are independently zero or one; and b) identifying at least one of the members of the plurality of

$CD4^+$ T cells that is specific for the peptide complexed with the MHC class II multimer. In some embodiments, R^1 is an amino acid sequence consisting of from 1 to 40 amino acids, and R^2 is an amino acid sequence consisting of from 1 to 40 amino acids.

[0192] In certain embodiments, the FVIII peptides disclosed herein can be used to generate reagents suitable for direct staining of FVIII specific T cells. For example, the MHC class II multimers that present the FVIII peptides of the present invention can include a variety of forms, such as a MHC class II tetramer. These MHC class II molecules can be further modified to include a diagnostic agent. Alternatively, the FVIII peptides that complex with the MHC class II multimers can include a diagnostic agent. The diagnostic agents (*i.e.*, a detectable moiety) used in the present invention can include those generally known in the art for immune monitoring. For example, FVIII-specific T cells can be identified and/or isolated based on detection of a diagnostic agent associated with a FVIII peptide described herein that is presented by an MHC class II tetramer. Suitable diagnostic agents can include a fluorescent agent, a chemiluminescent agent, a radioactive agent, a contrast agent, and the like. Suitable fluorescence agents include those typically used in flow cytometry and can include but are not limited to fluorescein isothiocyanate, R-Phycoerythrin, Texas Red, Cy3, Cy5, Cy5.5, Cy7, and derivatives thereof.

[0193] In certain embodiments, the FVIII peptide can be used to re-stimulate $CD4^+$ FVIII-specific T cells *in vitro*. In these embodiments, the re-stimulation of the T cells could be monitored by detection of proliferation, secretion of cytokines or chemokines, or the up- or down-regulation of certain activation markers that are known to those skilled in the art.

[0194] In some embodiments, detection of the diagnostic agent can be used to identify and/or isolate T cells specific for the FVIII peptides disclosed herein. For example, the reagents above (e.g., peptide, MHC class II tetramer, and diagnostic agent) can be used to track FVIII-specific T cells *in vitro* or *ex vivo*. In certain embodiments, the T cells can be further isolated and characterized using various techniques generally known in the art, such as flow cytometry, e.g., fluorescence activated cell sorting (FACS), and/or PCR, e.g., single cell PCR.

[0195] To carry out immune monitoring analyses, T cells that bind the FVIII peptide-MHC class II multimer complex include $CD4^+$ T cells and can be isolated from a patient using a variety of methods generally known in the art. For example, T cells can be isolated and purified from a patient's blood, organs or other tissue. Isolation and identification of the FVIII specific T cells can be used for a variety of immunodiagnostic applications. In certain embodiments, the

FVIII peptides or associated reagents can be used for immune monitoring of FVIII-specific T cells during clinical development of a new FVIII product. In other embodiments, the FVIII peptides can be used for immune monitoring of FVIII-specific T cells during immune tolerance induction therapy. In yet other embodiments, the FVIII peptides can be used for immune monitoring of FVIII-specific T cells during FVIII treatment.

VIII. Kits of the Invention

[0196] The present invention also provides kits to facilitate and/or standardize use of compositions provided by the present invention, as well as facilitate the methods of the present invention. Materials and reagents to carry out these various methods can be provided in kits to facilitate execution of the methods. As used herein, the term "kit" is used in reference to a combination of articles that facilitate a process, assay, analysis or manipulation.

[0197] Kits can contain chemical reagents (*e.g.*, FVIII peptides or polynucleotides encoding FVIII peptides) as well as other components. In addition, kits of the present invention can also include, for example but are not limited to, apparatus and reagents for sample collection and / or purification, apparatus and reagents for product collection and/or purification, reagents for bacterial cell transformation, reagents for eukaryotic cell transfection, previously transformed or transfected host cells, sample tubes, holders, trays, racks, dishes, plates, instructions to the kit user, solutions, buffers or other chemical reagents, suitable samples to be used for standardization, normalization, and / or control samples. Kits of the present invention can also be packaged for convenient storage and safe shipping, for example, in a box having a lid.

[0198] In some embodiments, for example, kits of the present invention can provide a FVIII peptide of the invention, a polynucleotide vector (*e.g.*, a plasmid) encoding a FVIII peptide of the invention, bacterial cell strains suitable for propagating the vector, and reagents for purification of expressed fusion proteins. Alternatively, a kit of the present invention can provide the reagents necessary to conduct mutagenesis of a FVIII peptide in order to generate a conservatively modified variant of the FVIII peptide.

[0199] A kit can contain one or more compositions of the invention, for example, one or a plurality of FVIII peptides or one or a plurality of polynucleotides that encode the FVIII peptides. Alternatively, a kit can contain reagents (*e.g.*, peptide, MHC class II tetramer, and diagnostic agent) for carrying out immune monitoring of a patient.

[0200] A kit of the invention also can contain one or a plurality of recombinant nucleic acid molecules, which encode the FVIII peptides, which can be the same or different, and can further include, for example, an operatively linked second polynucleotide containing or encoding a restriction endonuclease recognition site or a recombinase recognition site, or any polypeptide of interest. In addition, the kit can contain instructions for using the components of the kit, particularly the compositions of the invention that are contained in the kit.

IX. Specific Embodiments

[0201] In one embodiment, the present invention provides a FVIII peptide consisting of a consecutive sequence of nine amino acids that is at least 85 % identical to nine consecutive amino acids in the following amino acid sequence: QANRSPLPIAKVSSFPSIRPIYLT (SEQ ID NO:344), and the peptide has the formula: (R1)x-peptide-(R2)y, wherein R1 is an amino acid sequence consisting of from 1 to 80 amino acids; R2 is an amino acid sequence consisting of from 1 to 80 amino acids; and each of the subscripts x and y are independently zero or one.

[0202] In one embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 80 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 70 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 60 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 50 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 40 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 30 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 20 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 10 amino acids. In another embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 5 amino acids. In yet other embodiment, R^1 and R^2 are seperately or both amino acid sequences consisting of from 1 to 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, or 80 amino acids.

[0203] In a specific embodiment of the peptides described above, x and y are both zero.

[0204] In a specific embodiment of the peptides described above, x is one and y is zero.

[0205] In a specific embodiment of the peptides described above, x is zero and y is one.

[0206] In a specific embodiment of the peptides described above, x and y are both one.

[0207] In a specific embodiment of the peptides described above, the consecutive sequence of nine amino acids is identical to nine consecutive amino acids in the amino acid sequence: QANRSPLPIAKVSSFPSIRPIYLT (SEQ ID NO:344).

[0208] In one embodiment, the present invention provides a pharmaceutical composition comprising a FVIII peptide consisting of a consecutive sequence of nine amino acids that is at least 85 % identical to nine consecutive amino acids in the following amino acid sequence: QANRSPLPIAKVSSFPSIRPIYLT (SEQ ID NO:344), and the peptide has the formula: (R1)x-peptide-(R2)y, wherein R1 is an amino acid sequence consisting of from 1 to 80 amino acids; R2 is an amino acid sequence consisting of from 1 to 80 amino acids; and each of the subscripts x and y are independently zero or one.

[0209] In a specific embodiment of the compositions described above, x and y are both zero.

[0210] In a specific embodiment of the compositions described above, x is one and y is zero.

[0211] In a specific embodiment of the compositions described above, x is zero and y is one.

[0212] In a specific embodiment of the compositions described above, x and y are both one.

[0213] In a specific embodiment of the compositions described above, the composition further comprises at least one peptide consisting of a consecutive sequence of nine amino acids that is at least 85 % identical to nine consecutive amino acids in an amino acid sequence independently selected from the group consisting of GEVGDTLLIIFKNQASRPYNI (SEQ ID NO:159), PTKSDPRCLTRYYSSFVNMER (SEQ ID NO:250), EVEDNIMVTFRNQASRPYSFY (SEQ ID NO:477), LHAGMSTLFLVYSNKCQTPLG (SEQ ID NO:568), NPPIIARYIRLHPTHYSIRST (SEQ ID NO:659), TVVITLKNMASHPVSLHA (SEQ ID NO:10), AWPKMHTVNGYVNRSLPGLIG (SEQ ID NO:68), and TVVITLKNMASHPVSLHAVGV (SEQ ID NO:740), wherein the at least one peptide is a maximum of 80 amino acids in length and wherein any additional amino acids in the at least one peptide are natural amino acids.

[0214] In one embodiment, the present invention provides a method of inducing an immune tolerance to FVIII in a subject, the method comprising a step of administering to the subject a therapeutically effective amount of a pharmaceutical composition comprising a FVIII peptide consisting of a consecutive sequence of nine amino acids that is at least 85 % identical to nine consecutive amino acids in the following amino acid sequence: QANRSPLPIAKVSSFPSIRPIYLT (SEQ ID NO: 344), and the peptide has the formula: (R1)x-peptide-(R2)y, wherein R1 is an amino acid sequence consisting of from 1 to 80 amino acids; R2 is an amino acid sequence consisting of from 1 to 80 amino acids; each of the subscripts x and y are independently zero or one; and thereby inducing an immune tolerance to FVIII protein in the subject.

[0215] In a specific embodiment of the methods described above, the pharmaceutical composition further comprises at least one peptide consisting of a consecutive sequence of nine amino acids that is at least 85 % identical to nine consecutive amino acids in an amino acid sequence independently selected from the group consisting of GEVGDTLLIIFKNQASRPYNI (SEQ ID NO:159), PTKSDPRCLTRYYSSFVNMER (SEQ ID NO:250), EVEDNIMVTFRNQASRPYSFY (SEQ ID NO:477), LHAGMSTLFLVYSNKCQTPLG (SEQ ID NO:568), NPPIIARYIRLHPTHYSIRST (SEQ ID NO:659), TVVITLKNMASHPVSLHA (SEQ ID NO:10), AWPKMHTVNGYVNRSLPGLIG (SEQ ID NO:68), and TVVITLKNMASHPVSLHAVGV (SEQ ID NO:740), wherein the at least one peptide is a maximum of 80 amino acids in length and wherein any additional amino acids in the at least one peptide are natural amino acids.

[0216] In a specific embodiment of the methods described above, administration of the pharmaceutical composition prevents development anti-FVIII antibodies in the subject.

[0217] In a specific embodiment of the methods described above, administration of the pharmaceutical composition reduces an amount anti-FVIII antibodies present in the subject.

[0218] In a specific embodiment of the methods described above, x and y are both zero.

[0219] In a specific embodiment of the methods described above, x is one and y is zero.

[0220] In a specific embodiment of the methods described above, x is zero and y is one.

[0221] In a specific embodiment of the methods described above, x and y are both one.

[0222] In one embodiment, the present invention provides a method of making a FVIII peptide, the method comprising the steps of: a) providing a culture of cells comprising a vector that encodes a FVIII peptide consisting of a consecutive sequence of nine amino acids that is at least 85 % identical to nine consecutive amino acids in the following amino acid sequence: QANRSPLPIAKVSSFPSIRPIYLT (SEQ ID NO: 344), and the peptide has the formula: (R1)x-peptide-(R2)y wherein R1 is an amino acid sequence consisting of from 1 to 80 amino acids; R2 is an amino acid sequence consisting of from 1 to 80 amino acids; each of the subscripts x and y are independently zero or one; and b) expressing the peptide in the culture of cells.

[0223] In a specific embodiment of the methods described above, x and y are both zero.

[0224] In a specific embodiment of the methods described above, x is one and y is zero.

[0225] In a specific embodiment of the methods described above, x is zero and y is one.

[0226] In a specific embodiment of the methods described above, x and y are both one.

[0227] In one embodiment, the present invention provides a method of making a FVIII peptide, the method comprising: a) synthesizing a peptide using solid phase or liquid phase synthesis techniques, the peptide consisting of a consecutive sequence of nine amino acids that is at least 85 % identical to nine consecutive amino acids in the following amino acid sequence: QANRSPLPIAKVSSFPSIRPIYLT (SEQ ID NO: 344), and the peptide has the formula: (R1)x-peptide-(R2)y wherein R1 is an amino acid sequence consisting of from 1 to 80 amino acids; R2 is an amino acid sequence consisting of from 1 to 80 amino acids; and each of the subscripts x and y are independently zero or one.

[0228] In a specific embodiment of the methods described above, x and y are both zero.

[0229] In a specific embodiment of the methods described above, x is one and y is zero.

[0230] In a specific embodiment of the methods described above, x is zero and y is one.

[0231] In a specific embodiment of the methods described above, x and y are both one.

[0232] In one embodiment, the present invention provides a method of identifying FVIII peptide-specific T cells, the method comprising: a) combining a plurality of CD4+ T cells with a FVIII peptide complexed with a MHC class II multimer, the FVIII peptide consisting of a consecutive sequence of nine amino acids that is at least 85 % identical to nine consecutive

amino acids in the following amino acid sequence: QANRSPLPIAKVSSFPSIRPIYLT (SEQ ID NO: 344), and the peptide has the formula: (R1)x-peptide-(R2)y, wherein R1 is an amino acid sequence consisting of from 1 to 80 amino acids; R2 is an amino acid sequence consisting of from 1 to 80 amino acids; each of the subscripts x and y are independently zero or one; and b) identifying at least one of the members of the plurality of CD4+ T cells that is specific for the peptide complexed with the MHC class II multimer.

[0233] In a specific embodiment of the methods described above, the MHC class II multimer is a MHC class II tetramer.

[0234] In a specific embodiment of the methods described above, the peptide or MHC class II multimer further comprises a diagnostic agent.

[0235] In a specific embodiment of the methods described above, the diagnostic agent identifies the at least one member of the plurality of CD4+ T cells that is specific for the peptide.

[0236] In a specific embodiment of the methods described above, the method further comprises isolating the at least one member of the plurality of CD4+ T cells that is specific for the peptide based on detection of the diagnostic agent.

[0237] In a specific embodiment of the methods described above, the at least one member of the plurality of CD4+ T cells is isolated with flow cytometry.

[0238] In a specific embodiment of the methods described above, x and y are both zero.

[0239] In a specific embodiment of the methods described above, x is one and y is zero.

[0240] In a specific embodiment of the methods described above, x is zero and y is one.

[0241] In a specific embodiment of the methods described above, x and y are both one.

[0242] The present invention will now be further illustrated in the following examples, without being limited thereto.

X. EXAMPLES

Example 1

[0243] To better mimic the human MHC class II molecule for identifying FVIII peptides, a mouse model was developed for hemophilia A with a chimeric MHC class II molecule carrying a

human HLA-DRB1*1501 specific binding site. This mouse was backcrossed to a mouse carrying a complete knock out of all murine MHC class II genes (Reipert *et al.*, *J. Thromb. Haemost.* 7 Suppl. 1:92-97 (2009)). In this new transgenic mouse model, all $CD4^+$ T cell responses are driven by the human MHC class II molecule. This mouse model was used to identify FVIII peptides presented by HLA-DRB1*1501 that drive anti-FVIII immune responses in these mice.

Materials and Methods

[0244] FVIII: Recombinant human FVIII (rFVIII) was produced as an albumin free bulk product (Baxter Neuchatel) and clinical sucrose formulated FVIII product (Advate, Baxter, Westlake Village, CA).

[0245] Hemophilic HLA-DRB15 E17 mice: HLA-DRB1*1501$^{+/-}$ E17$^{-/-}$ mice as described in Reipert *et al.*, *J. Thromb. Haemost.* 7 Suppl. 1:92-97 (2009). Mice were all male and aged 8 to 12 weeks at the beginning of the experiment.

[0246] Immunization with human recombinant FVIII: HLA-DRB1*1501$^{+/-}$ E17$^{-/-}$ mice received between 4 and 8 intravenous or subcutaneous doses of 0.2 μg or 1 μg human rFVIII at weekly intervals. rFVIII was diluted in the original formulation buffer or Dulbecco phosphate buffered saline containing calcium and magnesium (DPBS; Sigma Aldrich, St. Louis, Missouri, USA).

[0247] Cell preparation: Spleens were obtained 3 to 7 days after the last immunization with rFVIII. Spleen cells were minced and passed through a 70 μm cell strainer (Becton Dickinson, Franklin Lakes, NJ). Single cells were collected in culture medium: RPMI 1640 medium (Gibco, Invitrogen, Life Technologies, Carlsbad, CA) supplemented with 10% preselected fetal calf serum (FCS; Hyclone, Logan, UT), 2 mM L-glutamine, 100 U/mL penicillin/streptomycin (both from Gibco), and $5x10^{-5}$ M mercaptoethanol (Sigma-Aldrich). Erythrocytes were lysed using hypotonic buffer (pH 7.2) composed of 0.15 M ammonium chloride, 10 mM potassium bicarbonate (both from Merck, Darmstadt, Germany) and 0.1 mM ethylene-diaminetetraacetic acid (Sigma-Aldrich). Cells were washed and counted using a Coulter Counter Z1.

Generation of T-cell hybridomas for identifying FVIII peptides

[0248] *In vitro* re-stimulation of spleen cells with human rFVIII: Spleen cells were re-stimulated in the presence of 20 μg/ml human FVIII in culture medium at a concentration of

$1.5x10^6$ cells/ml for 3 or 10 days. The culture medium for the 10 day cultures was renewed after 6 days.

[0249] Fusion of mouse T cells with BW cells: *In vitro* re-stimulated spleen cell cultures and BW cells (α-β-) were washed twice with serum free culture medium and then combined at a ratio of 1:3 to 1:10 (T cells : BW cells). The BW cell line was derived from a mouse AKR/J T cell lymphoma. These cells had no T cell receptors on their surface (α-β-) and therefore any T cell receptor after fusion with mouse spleen cells is derived from the fusion partner. After a third washing step, the supernatant was removed. Fusion conditions were achieved by the addition of 1 ml polyethyleneglycol (PEG; 50% HybiMax, Sigma-Aldrich) within 45 seconds. After another 45 seconds of incubation, subsequently 50 ml serum free medium were added to prevent the toxic effect of PEG. Cells were centrifuged at 1300 rpm for 5 minutes without a break to form a very firm pellet. The supernatant was discarded and 50 ml new serum free medium were added very slowly aiming not to dislocate the pellet. The tube was inverted slowly until the cells were re-suspended and centrifuged as before. This was done twice to remove the remaining PEG. The last washing step was done with culture medium. Cells were then diluted and cultured in 96 well plates. The culture medium was changed for selection medium (HAT medium supplement, Sigma Aldrich) after 48 hours and growing clones were selected. Selection medium was kept for 2 weeks, afterwards the medium was subsequently changed back to normal culture medium.

[0250] Peptide specificity of FVIII-specific T cell hybridomas: T cell hybridomas were tested for their antigen specificity. For this purpose, $1x10^5$ cells were co-cultured with antigen presenting cells. We used either $5x10^4$ Mgar cells (expressing HLA-DRB1*1501) or $1x10^5$ whole spleen cells derived from naïve HLA-DRB1*1501 – E17 mice. Cells were incubated with 10 µg/ml human rFVIII or with 1 µg/ml peptide/peptide pools for 24 hours at 37°C, 5%CO_2. The supernatants were collected and IL-2 release into the culture supernatant was measured using an IL-2 ELISA (BioLegend, San Diego, CA) or IL-2 Bio-Plex (Bio-Rad Laboratories, Hercules, CA) according to the manufacturers protocol. IL-2 release ≥ 20 pg/ml in the presence but not absence of FVIII (or peptides) was considered positive, or alternatively a 10 fold increase in IL-2 release in the presence of FVIII compared to the absence of FVIII was considered positive .

[0251] Subcloning of T cell hybridomas: To assure that each clone represents only one type of T cell, hybridoma all clones were sub-cloned. Hybridoma clones were diluted to a limiting

dilution of 0.3 cells/well and co-cultured with 200 feeder cells /well. Feeder cells were produced by Mitomycin C treatment of the fusion partner cells, BW cells. $2x10^8$ BW cells were treated with 0.1 mg Mitomycin C from *Streptomyces caespitosus* (Sigma Aldrich) for 10 minutes at room temperature and 25 minutes at 37°C, 5% CO_2 in the incubator. Five growing subclones per clone were selected and tested for their FVIII specificity.

[0252] FVIII peptide pools used to specify specificities of T cell hybridomas: FVIII peptide pools were produced using the SPOT synthesis method as described by Ay et al. (*Biopolymers* 88:64-75 (2007)). Briefly, 15 mer peptides were synthesized on two identical cellulose membranes. Membranes were cut into vertical and horizontal stripes. Peptides were released from the membrane stripes and used as peptide pools in specificity tests as described above. Peptides were dissolved in DMSO (Hybrimax, Sigma Aldrich) and further diluted with PBS.

Results

[0253] 181 FVIII specific hybridoma clones were produced. These clones were screened against a peptide library spanning the whole human FVIII. 15 mer peptides offset by three amino acids were used. Using this approach, six different FVIII regions that contained peptides bound to HLA-DRB1*1501 were identified. We found two peptide domains within the A1 domain, two peptides within the A2 domain, one within the B domain, two within the A3 domain and one peptide domain within the C1 domain of human FVIII. FVIII peptide$^{1401-1424}$ has not been described before (Table 11). Peptides FVIII$^{474-494}$, FVIII$^{545-559}$, FVIII$^{1788-1802}$ and FVIII$^{2161-2175}$ were already identified in WO 09/071886, which used computer prediction programs followed by the T cell hybridoma technology. Peptide FVIII$^{2030-2044}$ was disclosed in WO 03/087161. Peptide FVIII$^{2161-2180}$ was already published by Jacquemin *et al.*, Blood 101(4):1351-8 (2003).

Table 11. Regions of FVIII including T-cell epitopes

Regions including T cell epitopes	Amino Acid Sequence	**Disclosures**
FVIII$^{102-122}$	TVVITLKNMASHPVSLHAVGV (SEQ ID NO:740)	FVIII$^{107-121}$ disclosed in WO 2003/087161 FVIII$^{100-118}$ disclosed in WO/2009/095646

$FVIII^{246-266}$	AWPKMHTVNGYVNRSLPGLIG (SEQ ID NO:68)	$FVIII^{253-268}$ disclosed in WO/2009/095646
$FVIII^{474-494}$	GEVGDTLLIIFKNQASRPYNI (SEQ ID NO:159)	$FVIII^{475-495}$ Disclosed in WO 2009/071886 $FVIII^{477-495}$ disclosed in WO/2009/095646
$FVIII^{540-560}$	PTKSDPRCLTRYYSSFVNMER (SEQ ID NO:250)	FVIII $^{542-562}$ Disclosed in WO 2009/071886 $FVIII^{545-569}$ disclosed in WO/2009/095646
$FVIII^{1401-1424}$	QANRSPLPIAKVSSFPSIRPIYLT (SEQ ID NO:344)	A peptide of the present invention
$FVIII^{1785-1805}$	EVEDNIMVTFRNQASRPYSFY (SEQ ID NO:477)	FVIII $^{1785-1805}$ Disclosed in WO 2009/071886 $FVIII^{1787-1805}$ disclosed in WO/2009/095646
$FVIII^{2025-2045}$	LHAGMSTLFLVYSNKCQTPLG (SEQ ID NO:568)	FVIII $^{2030-2044}$ Disclosed in WO 2003/087161
$FVIII^{2160-2180}$	NPPIIARYIRLHPTHYSIRST (SEQ ID NO:659)	FVIII $^{2158-2178}$ Disclosed in WO 2009/071886 and FVIII $^{2161-2180}$ Jacquemin *et al.*, *supra*. FVIII $^{2164-2183}$ Disclosed in WO 2003/087161 FVIII $^{2164-2188}$ disclosed in WO/2009/095646

[0254] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

WHAT IS CLAIMED IS:

1. A method of inducing an immune tolerance to FVIII in a subject in need thereof, the method comprising a step of:

administering to the subject a therapeutically effective amount of a peptide having an amino acid sequence consisting of:

$$(R^1)_x\text{-}P\text{-}(R^2)_y,$$

wherein:

P is an amino acid sequence having at least 85% identity to at least nine consecutive amino acids of SEQ ID NO:344;

R^1 is an amino acid sequence consisting of from 1 to 80 amino acids;

R^2 is an amino acid sequence consisting of from 1 to 80 amino acids; and

each of x and y are independently zero or one.

2. The method of claim 1, wherein P is an amino acid sequence having at least 85% identity to a sequence of at least nine consecutive amino acids of SEQ ID NO:344.

3. The method of claim 1, wherein P is an amino acid sequence having at least 90% identity to a sequence of at least nine consecutive amino acids of SEQ ID NO:344.

4. The method of claim 1, wherein P is an amino acid sequence having at least 95% identity to a sequence of at least nine consecutive amino acids of SEQ ID NO:344.

5. The method of claim 1, wherein P is an amino acid sequence identical to a sequence of at least nine consecutive amino acids of SEQ ID NO:344.

6. The method according to any one of claims 1 to 5, wherein x and y are both zero.

7. The method according to any one of claims 1 to 5, wherein x is one and y is zero.

8. The method according to any one of claims 1 to 5, wherein x is zero and y is one.

9. The method according to any one of claims 1 to 5, wherein x and y are both one.

10. The method according to any one of claims 1 to 5, wherein the peptide consists of from 9 to 100 amino acids.

11. The method of claim 10, wherein the peptide consists of from 9 to 50 amino acids.

12. The method of claim 10, wherein the peptide consists of from 9 to 25 amino acids.

13. The method according to any one of claims 1 to 12, wherein the method further comprises a step of:

administering to the subject a therapeutically effective amount of a second peptide having an amino acid sequence consisting of:

$$(R^1)_x\text{-}P\text{-}(R^2)_y,$$

wherein:

P is an amino acid sequence having at least 85% identity to at least nine consecutive amino acids of a sequence selected from SEQ ID NOS:10, 68, 159, 250, 344, 477, 568, 659, and 740;

R^1 is an amino acid sequence consisting of from 1 to 80 amino acids;

R^2 is an amino acid sequence consisting of from 1 to 80 amino acids; and

each of x and y are independently zero or one.

14. The method according to any one of claims 1 to 13, wherein administration of the pharmaceutical composition prevents development of anti-FVIII antibodies in the subject.

15. The method according to any one of claims 1 to 13, wherein administration of the pharmaceutical composition reduces an amount anti-FVIII antibodies present in the subject.

16. A peptide consisting of the amino acid sequence:

$$(R^1)_x\text{-}P\text{-}(R^2)_y,$$

wherein:

P is an amino acid sequence having at least 85% identity to at least nine consecutive amino acids of SEQ ID NO:344;

R^1 is an amino acid sequence consisting of from 1 to 80 amino acids;

R^2 is an amino acid sequence consisting of from 1 to 80 amino acids; and

each of x and y are independently zero or one.

17. The peptide of claim 16, wherein P is an amino acid sequence having at least 85% identity to a sequence of at least nine consecutive amino acids of SEQ ID NO:344.

18. The peptide of claim 16, wherein P is an amino acid sequence having at least 90% identity to a sequence of at least nine consecutive amino acids of SEQ ID NO:344.

19. The peptide of claim 16, wherein P is an amino acid sequence having at least 95% identity to a sequence of at least nine consecutive amino acids of SEQ ID NO:344.

20. The peptide of claim 16, wherein P is an amino acid sequence identical to a sequence of at least nine consecutive amino acids of SEQ ID NO:344.

21. The peptide according to any one of claims 16 to 20, wherein x and y are both zero.

22. The peptide according to any one of claims 16 to 20, wherein x is one and y is zero.

23. The peptide according to any one of claims 16 to 20, wherein x is zero and y is one.

24. The peptide according to any one of claims 16 to 20, wherein x and y are both one.

25. The peptide according to any one of claims 16 to 20, wherein the peptide consists of from 9 to 100 amino acids.

26. The peptide of claim 25, wherein the peptide consists of from 9 to 50 amino acids.

27. The peptide of claim 25, wherein the peptide consists of from 9 to 25 amino acids.

28. A composition comprising a peptide according to any one of claims 16 to 27.

29. The composition of claim 28, wherein the composition is formulated for pharmaceutical administration.

30. The composition of claim 28 or 29, wherein the composition further comprises a second polypeptide, the second polypeptide consisting of the amino acid sequence:

$$(R^1)_x\text{-}P\text{-}(R^2)_y,$$

wherein:

P is an amino acid sequence having at least 85% identity to at least nine consecutive amino acids of a sequence selected from SEQ ID NOS:10, 68, 159, 250, 344, 477, 568, 659, and 740;

R^1 is an amino acid sequence consisting of from 1 to 80 amino acids;

R^2 is an amino acid sequence consisting of from 1 to 80 amino acids; and

each of x and y are independently zero or one.

31. A method of making a FVIII peptide, the method comprising the steps of:

a) providing a culture of cells comprising a polynucleotide that encodes a FVIII peptide according to any one of claims 16 to 27; and

b) expressing the peptide in the culture of cells.

32. A method of identifying a FVIII peptide-specific T cell, the method comprising:

a) combining a plurality of $CD4^+$ T cells with a peptide complexed with a MHC class II multimer, wherein the peptide is a FVIII peptide according to any one of claims 16 to 27; and

b) identifying at least one of the members of the plurality of $CD4^+$ T cells that is specific for the peptide complexed with the MHC class II multimer.

33. The method of claim 32, wherein the MHC class II multimer is a MHC class II tetramer.

34. The method of claim 32 or 33, wherein the peptide or MHC class II multimer further comprises a detectable moiety.

35. The method according to any one of claims 32 to 34, further comprising isolating the at least one $CD4^+$ T cell that is specific for the peptide.

36. The method of claim 35, wherein the $CD4^+$ T cell is isolated using flow cytometry.

37. A fusion protein comprising:
a Factor VIII peptide according to any one of claims 16 to 27; and
a second peptide.

38. The fusion protein of claim 37, wherein the second peptide is a reporter peptide.

39. The fusion protein of claim 37 or 38, wherein the fusion protein is encoded by a nucleic acid.

40. The fusion protein of claim 37 or 38, wherein the FVIII peptide is chemically linked to the second peptide.

SEQUENCE LISTING

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BAXTER HEALTHCARE S.A.

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