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(56) Related Art
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(54) Title: HUMAN ANTIBODIES TO BET V 1 AND METHODS OF USE THEREOF

(57) Abstract: Provided herein are antibodies that bind Fagales allergens, Fagales related allergens, birch pollen, or Bet v 1, compositions comprising the antibodies, nucleic acids encoding the antibodies, and methods of using the antibodies. According to certain embodiments, the antibodies are fully human monoclonal antibodies that bind to Bet v 1. The antibodies are useful for binding Bet v 1 in vivo, thus preventing binding of the allergen to pre-formed IgE on the surface of mast cells or basophils. In doing so, the antibodies act to prevent the release of histamine and other inflammatory mediators from mast cells and/or basophils, thus ameliorating the untoward response to the Fagales allergens in sensitized individuals.

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HUMAN ANTIBODIES TO BET V 1 AND METHODS OF USE THEREOF

FIELD OF THE INVENTION

[0001] The present invention is generally related to human antibodies and antigen-binding fragments of human antibodies that bind to the birch pollen allergen, Bet v 1, therapeutic compositions comprising the antibodies, and methods of using the antibodies.

SEQUENCE LISTING

[0002] An official copy of the sequence listing is submitted concurrently with the specification electronically via EFS-Web as an ASCII formatted sequence listing with a file name of 10301WO01_SEQ_LIST_ST25, a creation date of May 31, 2018, and a size of about 137 kilobytes. The sequence listing contained in this ASCII formatted document is part of the specification and is herein incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

[0003] Birch is the predominant trigger in 23% of US and 14% of European allergy patients (Datamonitor report on Allergic Rhinitis, July 2010), and the main cause of type 1 allergies in the spring across Europe, North America, Russia, and Australia (Breiteneder et al., *EMBO J.* 1989, 8(7):1935-8). Bet v 1 protein is a major birch allergen identified in pollen from Betula verrucosa (European white birch tree, also synonymous with Betula pendula), and is responsible for IgE binding in more than 95% of birch pollen allergic patients (Breiteneder, supra). Bet v 1 is a small, 7-stranded anti-parallel β sheet with three α helices and a known crystalline structure (Kofler et al., 2012, 422(1): 109-23; Markovic-Housley et al., J Mol Biol. 2003, 325(1): 123-33; Spangfort et al., J Immunol. 2003, 171(6): 3084-90). WO 94/10194 relates to peptides derived from trees of the Fagales order.

[0004] Sixty percent of birch pollen allergic patients react exclusively to Bet v 1 (Jarolim et al., Int Arch Allergy Appl Immunol. 1989, 88(1-2): 180-2). A single birch tree can produce up to five million pollen grains which travel by air up to 100 yards from the tree. Symptoms of birch pollen allergy can range from mild rhinitis and conjunctivitis to life-threatening asthmatic responses.

[0005] Immunoglobulin E (IgE) is responsible for type 1 hypersensitivity, which manifests itself in allergic rhinitis, allergic conjunctivitis, hay fever, allergic asthma, bee venom allergy, and food allergies. IgE circulates in the blood and binds to high-affinity

FcεR1α receptors for IgE on basophils and mast cells. In most allergic responses, the allergens enter the body through inhalation, ingestion, or through the skin. The allergen then binds to preformed IgE already bound to the high affinity receptor on the surfaces of mast cells and basophils, resulting in cross-linking of several IgE molecules and triggering the release of histamine and other inflammatory mediators causing the various allergic symptoms.

[0006] The treatment for allergies includes steroids for suppressing the immune activity and bronchial dilators for relieving asthma symptoms. Desensitization therapy is also used for severely allergic patients. Peptide vaccine combinations have been tested for desensitizing individuals to particular allergens, *e.g.* Bet v 1 (See U.S. 9,017,689). Antibodies have been proposed as a treatment for allergies, since they may be able to block the entry of allergenic molecules into the mucosal tissues, or may bind the allergen before it has the opportunity to bind to the IgE bound to the high affinity receptor on mast cells or basophils, thus preventing the release of histamine and other inflammatory mediators from these cells.

[0007] U.S. patent number 5,670,626 describes the use of monoclonal antibodies for the treatment of IgE-mediated allergic diseases such as allergic rhinitis, allergic asthma, and allergic conjunctivitis by blocking the binding of allergens to the mucosal tissue. U.S. patent number 6,849,259 describes the use of allergen-specific antibodies to inhibit allergic inflammation in an *in vivo* mouse model of allergy. Milk-based and egg-based antibody systems have been described. For example, US2003/0003133A1 discloses using milk as a carrier for allergens for inducing oral tolerance to birch pollen and other allergens. Compositions and methods for reducing an allergic response in an animal to an allergen in the environment through use of a molecule that inhibits the ability of the allergen to bind to mast cells were described in WO1994/024164A2. Other antibodies to Bet v 1 were mentioned in U.S. 2010/0034812.

[0008] The present invention is directed toward overcoming one or more of the problems discussed above; and/or at least providing the public with a useful choice.

BRIEF SUMMARY OF THE INVENTION

[0009] Described herein are fully human monoclonal antibodies and antigen-binding fragments thereof that bind birch pollen, e.g. natural Bet v 1, Betula pendula birch pollen extract (BPE), Betula nigra BPE, or Betula populifolia BPE. The antibodies can be useful to bind the Bet v 1 allergen *in vivo* following exposure of a sensitized patient to the birch

allergen, and as such, may act to either promote clearance of natural Bet v 1, Betula pendula birch pollen extract (BPE), Betula nigra BPE, or Betula populifolia BPE or to block the binding of the allergen to pre-formed IgE on the surface of mast cells or basophils. By doing so, the antibodies described herein can prevent the release of histamine or other inflammatory mediators from mast cells or basophils, thereby preventing or diminishing the untoward effects observed in patients sensitized to the birch allergen. In certain embodiments, the antibodies may be capable of reducing, minimizing, or preventing at least one symptom in a patient sensitive to a birch allergen or birch-related allergen, such as sneezing, congestion, nasal blockage, coughing, wheezing, bronchoconstriction, rhinitis, or conjunctivitis. In some embodiments, the antibodies may be capable of preventing even more serious *in vivo* complications associated with exposure to the birch pollen allergen in sensitized individuals, such as asthmatic responses, anaphylaxis, or even death.

[0010] The antibodies described herein can be full-length, for example, an IgG1 or and IgG4 antibody, or may comprise only an antigen-binding portion, for example, a Fab, $F(ab')_2$, or scFv fragment, and can be modified to affect functionality, e.g., to eliminate residual effector functions (Reddy *et al.*, 2000, *J. Immunol.* 164: 1925-1933).

[0010a] A first aspect of the invention provides an isolated monoclonal antibody or antigen-binding fragment thereof that binds to natural Bet v 1 or birch pollen extract (BPE), wherein the antibody or fragment thereof comprises:

(a) a heavy chain complementarity determining region (HCDR)1 comprising the amino acid sequence of SEQ ID NO: 292; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 294; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 296; a light chain complementarity determining region (LCDR)1 comprising the amino acid sequence of SEQ ID NO: 300; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 302; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 304; or

(b) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 148; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 150; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 152; an LCDR1 comprising the amino acid sequence of SEQ ID NO: 156; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 158; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 160; or

(c) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 100; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 102; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 104; an LCDR1 comprising the amino acid sequence of SEQ

ID NO: 108; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 110; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 112; or

(d) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 116; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 118; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 120; an LCDR1 comprising the amino acid sequence of SEQ ID NO: 124; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 126; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 128; or

(e) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8; an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16; or

(f) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 20; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 22; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 24; an LCDR1 comprising the amino acid sequence of SEQ ID NO: 28; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 30; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 32; or

(g) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 36; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 38; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 40; an LCDR1 comprising the amino acid sequence of SEQ ID NO: 44; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 46; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 48; or

(h) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 52; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 54; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 56; an LCDR1 comprising the amino acid sequence of SEQ ID NO: 60; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 62; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 64; or

(i) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 68; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 70; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 72; an LCDR1 comprising the amino acid sequence of SEQ ID NO: 76; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 78; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 80; or

(j) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 84; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 86; an HCDR3 comprising the amino

acid sequence of SEQ ID NO: 88; an LCDR1 comprising the amino acid sequence of SEQ ID NO: 92; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 94; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 96; or

(k) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 132; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 134; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 136; an LCDR1 comprising the amino acid sequence of SEQ ID NO: 140; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 142; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 144; or

(l) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 164; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 166; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 168; an LCDR1 comprising the amino acid sequence of SEQ ID NO: 172; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 174; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 176; or

(m) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 180; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 182; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 184; an LCDR1 comprising the amino acid sequence of SEQ ID NO: 188; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 190; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 192; or

(n) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 196; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 198; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 200; an LCDR1 comprising the amino acid sequence of SEQ ID NO: 204; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 206; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 208; or

(o) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 212; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 214; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 216; an LCDR1 comprising the amino acid sequence of SEQ ID NO: 220; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 222; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 224; or

(p) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 228; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 230; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 232; an LCDR1 comprising the amino acid sequence of SEQ ID NO: 236; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 238; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 240; or

(q) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 244; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 246; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 248; an LCDR1 comprising the amino acid sequence of SEQ ID NO: 252; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 254; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 256; or

(r) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 260; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 262; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 264; an LCDR1 comprising the amino acid sequence of SEQ ID NO: 268; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 270; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 272; or

(s) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 276; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 278; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 280; an LCDR1 comprising the amino acid sequence of SEQ ID NO: 268; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 270; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 272; or

(t) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 284; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 286; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 288; an LCDR1 comprising the amino acid sequence of SEQ ID NO: 268; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 270; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 272.

[0010b] In another aspect, the invention provides a pharmaceutical composition comprising a therapeutically effective amount of an antibody or antigen-binding fragment of the invention and a pharmaceutically acceptable excipient.

[0010c] In another aspect, the invention provides a method of preventing or reducing mast cell degranulation or blocking basophil activation associated with natural Bet v 1, Betula pendula BPE, Betula nigra BPE, or Betula populifolia BPE sensitization, the method comprising administering an antibody or antigen-binding fragment thereof of the invention or a pharmaceutical composition of the invention to a patient in need thereof.

[0010d] In another aspect, the invention relates to use of an antibody or an antigen-binding fragment thereof of the invention, or a pharmaceutical composition of the invention, in the manufacture of a medicament for use in preventing or reducing mast cell degranulation or blocking basophil activation associated with natural Bet v 1, Betula pendula BPE, Betula nigra BPE, or Betula populifolia BPE sensitization.

[0010d] In another aspect, the invention provides a method for treating a patient who demonstrates a sensitivity to, or an allergic reaction against, a Fagales protein, a Fagales allergen, birch pollen or an extract thereof, or Bet v 1 protein, or for treating at least one symptom or complication associated with a sensitivity to, or allergic reaction against a Fagales protein, a Fagales allergen, birch pollen or an extract thereof, or Bet v 1 protein, the method comprising administering an effective amount of one or more isolated human monoclonal antibodies or antigen-binding fragments thereof of the invention, or a pharmaceutical composition of the invention, to a patient in need thereof, wherein the sensitivity to, or an allergic reaction against, a Fagales protein, a Fagales related allergen, birch pollen or an extract thereof, or Bet v 1 protein is either prevented, or lessened in severity and/or duration, or at least one symptom or complication associated with the sensitivity to, or allergic reaction against, a Fagales protein, a Fagales related allergen, birch pollen or an extract thereof, or Bet v 1 protein is prevented, or ameliorated, or that the frequency and/or duration of, or the severity of the sensitivity to or allergic reaction against, a Fagales protein, a Fagales related allergen, birch pollen or an extract thereof, or Bet v 1 protein is reduced following administration of one or more of the isolated human monoclonal antibodies or fragments thereof that bind Bet v 1, or following administration of a composition comprising any one or more of the foregoing antibodies.

[0010e] In another aspect, the invention relates to use of an antibody or antigen-binding fragment thereof of the invention, or a pharmaceutical composition of the invention in the manufacture of a medicament for use in treating a patient who demonstrates a sensitivity to, or an allergic reaction against, a Fagales protein, a Fagales allergen, birch pollen or an extract thereof, or Bet v 1 protein, or for treating at least one symptom or complication associated with a sensitivity to, or allergic reaction against a Fagales protein, a Fagales allergen, birch pollen or an extract thereof, or Bet v 1 protein.

[0010f] In another aspect, the invention provides a method for enhancing the efficacy and/or safety of an allergen-specific immunotherapy (SIT) regimen, the method comprising administering an effective amount of one or more antibodies or antigen-binding fragments thereof of the invention, or a pharmaceutical composition of the invention, to a patient in need thereof just prior to or concurrent with the SIT regimen, wherein the severity of an allergic reaction to the SIT regimen is mitigated.

[0010g] In another aspect, the invention relates to use of an antibody or antigen-binding fragment thereof of the invention, or a pharmaceutical composition of the invention,

in the manufacture of a medicament for use in enhancing the efficacy and/or safety of an allergen-specific immunotherapy (SIT) regimen.

[0010h] In another aspect, the invention provides a nucleic acid molecule encoding the human monoclonal antibody or antigen-binding fragment thereof of the invention.

[0010i] In another aspect, the invention provides an expression vector comprising the nucleic acid molecule of the invention.

[0010j] In another aspect, the invention provides a host cell containing the expression vector of the invention.

[0010k] In the description in this specification reference may be made to subject matter that is not within the scope of the claims of the current application. That subject matter should be readily identifiable to a person skilled in the art and may assist in putting into practice the invention as defined in the claims of this application.

BRIEF DESCRIPTION OF THE INVENTION

[0011] Described herein is an isolated human monoclonal antibody or antigen-binding fragment thereof that binds natural Bet v 1, Betula pendula birch pollen extract (BPE), Betula nigra BPE, and/or Betula populifolia BPE.

[0012] In one embodiment, the isolated human monoclonal antibody or antigen-binding fragment thereof inhibits natural Bet v 1, Betula pendula BPE, Betula nigra BPE, or Betula populifolia BPE binding to allergen specific IgE.

[0013] In one embodiment, the isolated human antibody or antigen-binding fragment thereof binds to Bet v 1 with a K_D equal to or less than 10^{-8} M. In one embodiment, the human antibody or antigen-binding fragment thereof binds to Bet v 1 with a K_D ranging from about 10^{-8} to about 10^{-11} M. In one embodiment, the isolated human antibody or antigen-binding fragment thereof binds to Bet v 1 with a K_D equal to or less than 27.9 nM. In one embodiment, the isolated human antibody or antigen-binding fragment thereof binds to Bet v 1 with a K_D equal ranging from about 0.66 nM to about 27.9 nM.

[0014] In one embodiment, the isolated human antibody is a fully human monoclonal antibody.

[0015] In one embodiment, the isolated human monoclonal antibody or antigen-binding fragment thereof cross-reacts with one or more allergens selected from the group consisting of Aln g1, Cor a1, Car b1, Que a1, Api g2, Api g1, Dau c1, Mal d1, Ost c1, Fag s1, and Cas s1. Such allergens can also be termed PR-10 proteins, or so-called pathogenesis-

related (PR) proteins. Additional PR-10 proteins (Bet v 1 family members) also include Act c 8 and Act d 8 (kiwi), Ara h 8 (peanut), Pru ar 1 (apricot), Pru av 1 (cherry), Pru p 1 (peach), Pyr c 1 (pear), Gly m 4 (soybean), Vig r 1 (mung bean), Sola I 4 (tomato), Cuc m 3 (melon), Rub i 1 (raspberry), and Fra a 1 (strawberry). These allergens can also be considered Fagales related allergens.

[0016] In one embodiment, the antibody or antigen-binding fragment thereof cross-reacts with one or more allergens selected from the group consisting of Aln g1, Mal d1, Api g1, Car b1, and Cor a1.

[0017] In one embodiment, the isolated human antibody or antigen-binding fragment thereof comprises the three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within any one of the heavy chain variable region (HCVR) sequences selected from the group consisting of SEQ ID NOs: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 282, and 290; and the three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within any one of the light chain variable region (LCVR) sequences selected from the group consisting of SEQ ID NOs: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, and 298. Methods and techniques for identifying CDRs within HCVR and LCVR amino acid sequences are well known in the art and can be used to identify CDRs within the specified HCVR and/or LCVR amino acid sequences disclosed herein. Exemplary conventions that can be used to identify the boundaries of CDRs include, *e.g.*, the Kabat definition, the Chothia definition, and the AbM definition. In general terms, the Kabat definition is based on sequence variability, the Chothia definition is based on the location of the structural loop regions, and the AbM definition is a compromise between the Kabat and Chothia approaches. *See*, *e.g.*, Kabat, "Sequences of Proteins of Immunological Interest," National Institutes of Health, Bethesda, Md. (1991); Al-Lazikani *et al.*, (1997), *J. Mol. Biol. 273*:927-948; and Martin *et al.*, (1989), *Proc. Natl. Acad. Sci. USA 86*:9268-9272. Public databases are also available for identifying CDR sequences within an antibody.

[0018] In one embodiment, the isolated human antibody or antigen-binding fragment thereof comprises the three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within any one of the heavy chain variable region (HCVR) sequences selected from the group consisting of SEQ ID NOs: 114, 146, 98, and 290; and the three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within any one of the light chain variable region (LCVR) sequences selected from the group consisting of SEQ ID NOs: 122, 154, 106, and 298.

[0019] In one embodiment, the isolated human antibody or antigen-binding fragment thereof comprises a HCVR having an amino acid sequence selected from the group

consisting of SEQ ID NOs: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 282, and 290.

[0020] In one embodiment, the isolated human antibody or antigen-binding fragment thereof comprises a HCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs: 114, 146, 98, and 290.

[0021] In one embodiment, the isolated human antibody or antigen-binding fragment thereof comprises a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, and 298.

[0022] In one embodiment, the isolated human antibody or antigen-binding fragment thereof comprises a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs: 122, 154, 106, and 298.

[0023] In one embodiment, the isolated human antibody or antigen-binding fragment thereof comprises: (a) a HCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 282, and 290; and (b) a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NO: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, and 298.

[0024] In one embodiment, the isolated human antibody or antigen-binding fragment thereof comprises: (a) a HCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs: 114, 146, 98, and 290; and (b) a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NO: 122, 154, 106, and 298.

[0025] In one embodiment, the isolated human antibody or antigen-binding fragment thereof comprises:

(a) a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 20, 36, 52, 68, 84, 100, 116, 132, 148, 164, 180, 196, 212, 228, 244, 260, 276, 284, and 292;

(b) a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 22, 38, 54, 70, 86, 102, 118, 134, 150, 166, 182, 198, 214, 230, 246, 262, 278, 286, and 294;

(c) a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 24, 40, 56, 72, 88, 104, 120, 136, 152, 168, 184, 200, 216, 232, 248, 264, 280, 288, and 296;

(d) a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 28, 44, 60, 76, 92, 108, 124, 140, 156, 172, 188, 204, 220, 236, 252, 268, and 300;

(e) a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 30, 46, 62, 78, 94, 110, 126, 142, 158, 174, 190, 206, 222, 238, 254, 270, and 302; and

(f) a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 16, 32, 48, 64, 80, 96, 112, 128, 144, 160, 176, 192, 208, 224, 240, 256, 272, and 304.

[0026] In one embodiment, the isolated human antibody or antigen-binding fragment thereof comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/266, 282/266, and 290/298.

[0027] In one embodiment, the isolated human antibody or antigen-binding fragment thereof comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 114/122, 146/154, 98/106, and 290/298.

[0028] In one embodiment, the isolated human antibody or antigen-binding fragment thereof which binds to Bet v 1 comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 146/154 and 290/298.

[0029] In one embodiment, the isolated human antibody or antigen-binding fragment thereof which binds to Bet v 1 interacts with at least one amino acid sequence selected from the group consisting of amino acid residues ranging from about position 23 to about position 44 of SEQ ID NO: 306; amino acid residues ranging from about position 44 to about 70 of SEQ ID NO: 306; amino acid residues ranging from about 2 to about 19 of SEQ ID NO: 306; amino acid residues ranging from about 57 to about 70 of SEQ ID NO: 306; and amino acid residues ranging from about 81 to about 96 of SEQ ID NO: 306.

[0030] In one embodiment, the isolated human antibody or antigen-binding fragment thereof which binds to Bet v 1 interacts with amino acid residues ranging from about position 23 to about position 44 of SEQ ID NO: 306.

[0031] In one embodiment, the isolated human antibody or antigen-binding fragment thereof which binds to Bet v 1 interacts with amino acid residues ranging from about position 23 to about position 43 of SEQ ID NO: 306.

[0032] In one embodiment, the isolated human antibody or antigen-binding fragment thereof which binds to Bet v 1 interacts with amino acid residues ranging from about position 44 to about position 70 of SEQ ID NO: 306.

[0033] In one embodiment, the isolated human antibody or antigen-binding fragment thereof which binds to Bet v 1 interacts with amino acid residues ranging from about position 44 to about position 56 of SEQ ID NO: 306.

[0034] In one embodiment, the isolated human antibody or antigen-binding fragment thereof which binds to Bet v 1 interacts with amino acid residues ranging from about position 2 to about position 19 of SEQ ID NO: 306.

[0035] In one embodiment, the isolated human antibody or antigen-binding fragment thereof which binds to Bet v 1 interacts with amino acid residues ranging from about position 57 to about position 70 of SEQ ID NO: 306.

[0036] In one embodiment, the isolated human antibody or antigen-binding fragment thereof which binds to Bet v 1 interacts with amino acid residues ranging from about position 57 to about position 66 of SEQ ID NO: 306.

[0037] In one embodiment, the isolated human antibody or antigen-binding fragment thereof which binds to Bet v 1 interacts with amino acid residues ranging from about position 81 to about position 96 of SEQ ID NO: 306.

[0038] In one embodiment, the isolated human antibody or antigen-binding fragment thereof which binds to Bet v 1 interacts with amino acid residues ranging from about position 81 to about position 89 of SEQ ID NO: 306.

[0039] In one embodiment, the isolated human antibody or antigen-binding fragment thereof which binds to Bet v 1 interacts with at least one amino acid sequence selected from the group consisting of SEQ ID NO: 307, 308, 309, 310, and 311. The epitopes comprising SEQ ID NOs: 307, 308, 309, 310, or 311 can be extended by 1 to 5 amino acids, or 5 to 10 amino acids, on either the C-terminal end or the N-terminal end. For example, the epitope of SEQ ID NO: 311 when extended by 5 to 10 amino acids encompasses the epitope of SEQ ID NO: 115. In other words, an epitope comprising SEQ ID NO: 311, for example, includes the epitope of SEQ ID NO: 315.

[0040] In one embodiment, the isolated human antibody or antigen-binding fragment thereof which binds to Bet v 1 interacts with SEQ ID NO: 307.

[0041] In one embodiment, the isolated human antibody or antigen-binding fragment thereof which binds to Bet v 1 interacts with SEQ ID NO: 308.

[0042] In one embodiment, the isolated human antibody or antigen-binding fragment thereof which binds to Bet v 1 interacts with SEQ ID NO: 309.

[0043] In one embodiment, the isolated human antibody or antigen-binding fragment thereof which binds to Bet v 1 interacts with SEQ ID NO: 310.

[0044] In one embodiment, the isolated human antibody or antigen-binding fragment thereof which binds to Bet v 1 interacts with SEQ ID NO: 311.

[0045] In one embodiment, the isolated human antibody or antigen-binding fragment thereof which binds to Bet v 1 interacts with SEQ ID NO: 315.

[0046] In one embodiment, the isolated human antibody or antigen binding fragment thereof which binds to Bet v 1 interacts with at least one amino acid sequence selected from the group consisting of SEQ ID NOs: 307, 308, 309, 310, 311, and 315 and comprises an HCVR/LCVR sequence pair selected from the group consisting of SEQ ID NOs: 114/122, 146/154, 98/106, and 290/298.

[0047] In one embodiment, the isolated human antibody or antigen binding fragment thereof that interacts with SEQ ID NO: 307 comprises the three HCDRs contained in the heavy chain variable region of SEQ ID NO: 146 and the three LCDRs contained in the light chain variable region of SEQ ID NO: 154.

[0048] In one embodiment, the isolated human antibody or antigen binding fragment thereof that interacts with SEQ ID NO: 310 comprises the three HCDRs contained in the heavy chain variable region of SEQ ID NO: 290 and the three LCDRs contained in the light chain variable region of SEQ ID NO: 298.

[0049] In one embodiment, the human antibody or antigen binding fragment thereof that binds Bet v 1 comprises the HCDR1, HCDR2 and HCDR3 amino acid sequences of SEQ ID NO: 148, 150, and 152, respectively and LCDR1, LCDR2 and LCDR3 amino acid sequences of SEQ ID NO: 156, 158, and 160, respectively.

[0050] In one embodiment, the human antibody or antigen binding fragment thereof that binds to Bet v 1 comprises the HCDR1, HCDR2 and HCDR3 amino acid sequences of SEQ ID NO: 292, 294, and 296, respectively and LCDR1, LCDR2 and LCDR3 amino acid sequences of SEQ ID NO: 300, 302, and 304, respectively.

[0051] In one embodiment, the human antibody or antigen binding fragment thereof that binds to Bet v 1 comprises the HCDR1, HCDR2 and HCDR3 amino acid sequences of SEQ ID NO: 4, 6, and 8, respectively and LCDR1, LCDR2 and LCDR3 amino acid sequences of SEQ ID NO: 12, 14, and 16, respectively.

[0052] In one embodiment, the human antibody or antigen binding fragment thereof that binds to Bet v 1 comprises the HCDR1, HCDR2 and HCDR3 amino acid sequences of SEQ ID NO: 20, 22, and 24, respectively and LCDR1, LCDR2 and LCDR3 amino acid sequences of SEQ ID NO: 28, 30, and 32, respectively.

[0053] In one embodiment, the human antibody or antigen binding fragment thereof that binds to Bet v 1 comprises the HCDR1, HCDR2 and HCDR3 amino acid sequences of SEQ ID NO: 36, 38, and 40, respectively and LCDR1, LCDR2 and LCDR3 amino acid sequences of SEQ ID NO: 44, 46, and 48, respectively.

[0054] In one embodiment, the human antibody or antigen binding fragment thereof that binds to Bet v 1 comprises the HCDR1, HCDR2 and HCDR3 amino acid sequences of SEQ ID NO: 52, 54, and 56, respectively and LCDR1, LCDR2 and LCDR3 amino acid sequences of SEQ ID NO: 60, 62, and 64, respectively.

[0055] In one embodiment, the human antibody or antigen binding fragment thereof that binds to Bet v 1 comprises the HCDR1, HCDR2 and HCDR3 amino acid sequences of SEQ ID NO: 68, 70, and 72, respectively and LCDR1, LCDR2 and LCDR3 amino acid sequences of SEQ ID NO: 76, 78, and 80, respectively.

[0056] In one embodiment, the human antibody or antigen binding fragment thereof that binds to Bet v 1 comprises the HCDR1, HCDR2 and HCDR3 amino acid sequences of SEQ ID NO: 84, 86, and 88, respectively and LCDR1, LCDR2 and LCDR3 amino acid sequences of SEQ ID NO: 92, 94, and 96, respectively.

[0057] In one embodiment, the human antibody or antigen binding fragment thereof that binds to Bet v 1 comprises the HCDR1, HCDR2 and HCDR3 amino acid sequences of SEQ ID NO: 100, 102, and 104, respectively and LCDR1, LCDR2 and LCDR3 amino acid sequences of SEQ ID NO: 108, 110, and 112, respectively.

[0058] In one embodiment, the human antibody or antigen binding fragment thereof that binds to Bet v 1 comprises the HCDR1, HCDR2 and HCDR3 amino acid sequences of SEQ ID NO: 116, 118, and 120, respectively and LCDR1, LCDR2 and LCDR3 amino acid sequences of SEQ ID NO: 124, 126, and 128, respectively.

[0059] In one embodiment, the human antibody or antigen binding fragment thereof that binds to Bet v 1 comprises the HCDR1, HCDR2 and HCDR3 amino acid sequences of SEQ ID NO: 132, 134, and 136, respectively and LCDR1, LCDR2 and LCDR3 amino acid sequences of SEQ ID NO: 140, 142, and 144, respectively.

[0060] In one embodiment, the human antibody or antigen binding fragment thereof that binds to Bet v 1 comprises the HCDR1, HCDR2 and HCDR3 amino acid sequences of

SEQ ID NO: 164, 166, and 168, respectively and LCDR1, LCDR2 and LCDR3 amino acid sequences of SEQ ID NO: 172, 174, and 176, respectively.

[0061] In one embodiment, the human antibody or antigen binding fragment thereof that binds to Bet v 1 comprises the HCDR1, HCDR2 and HCDR3 amino acid sequences of SEQ ID NO: 180, 182, and 184, respectively and LCDR1, LCDR2 and LCDR3 amino acid sequences of SEQ ID NO: 188, 190, and 192, respectively.

[0062] In one embodiment, the human antibody or antigen binding fragment thereof that binds to Bet v 1 comprises the HCDR1, HCDR2 and HCDR3 amino acid sequences of SEQ ID NO: 196, 198, and 200, respectively and LCDR1, LCDR2 and LCDR3 amino acid sequences of SEQ ID NO: 204, 206, and 208, respectively.

[0063] In one embodiment, the human antibody or antigen binding fragment thereof that binds to Bet v 1 comprises the HCDR1, HCDR2 and HCDR3 amino acid sequences of SEQ ID NO: 212, 214, and 216, respectively and LCDR1, LCDR2 and LCDR3 amino acid sequences of SEQ ID NO: 220, 222, and 224, respectively.

[0064] In one embodiment, the human antibody or antigen binding fragment thereof that binds to Bet v 1 comprises the HCDR1, HCDR2 and HCDR3 amino acid sequences of SEQ ID NO: 228, 230, and 232, respectively and LCDR1, LCDR2 and LCDR3 amino acid sequences of SEQ ID NO: 236, 238, and 234, respectively.

[0065] In one embodiment, the human antibody or antigen binding fragment thereof that binds to Bet v 1 comprises the HCDR1, HCDR2 and HCDR3 amino acid sequences of SEQ ID NO: 244, 246, and 248, respectively and LCDR1, LCDR2 and LCDR3 amino acid sequences of SEQ ID NO: 252, 254, and 256, respectively.

[0066] In one embodiment, the human antibody or antigen binding fragment thereof that binds to Bet v 1 comprises the HCDR1, HCDR2 and HCDR3 amino acid sequences of SEQ ID NO: 260, 262, and 264, respectively and LCDR1, LCDR2 and LCDR3 amino acid sequences of SEQ ID NO: 268, 270, and 272, respectively.

[0067] In one embodiment, the human antibody or antigen binding fragment thereof that binds to Bet v 1 comprises the HCDR1, HCDR2 and HCDR3 amino acid sequences of SEQ ID NO: 276, 278, and 280, respectively and LCDR1, LCDR2 and LCDR3 amino acid sequences of SEQ ID NO: 268, 270, and 272, respectively.

[0068] In one embodiment, the human antibody or antigen binding fragment thereof that binds to Bet v 1 comprises the HCDR1, HCDR2 and HCDR3 amino acid sequences of SEQ ID NO: 284, 286, and 288, respectively and LCDR1, LCDR2 and LCDR3 amino acid sequences of SEQ ID NO: 268, 270, and 272, respectively.

[0069] In one embodiment, described is a fully human monoclonal antibody or antigen-binding fragment thereof that binds to natural Bet v 1, Betula pendula birch BPE, Betula nigra BPE, or Betula populifolia BPE, wherein the antibody or fragment thereof exhibits one or more of the following characteristics: (i) comprises a HCVR having an amino acid sequence selected from the group consisting of SEQ ID NO: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 282, and 290, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (ii) comprises a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NO: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, and 298, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (iii) comprises a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 8, 24, 40, 56, 72, 88, 104, 120, 136, 152, 168, 184, 200, 216, 232, 248, 264, 280, 288, and 296, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 16, 32, 48, 64, 80, 96, 112, 128, 144, 160, 176, 192, 208, 224, 240, 256, 272, and 304, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (iv) comprises a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 4, 20, 36, 52, 68, 84, 100, 116, 132, 148, 164, 180, 196, 212, 228, 244, 260, 276, 284, and 292, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 6, 22, 38, 54, 70, 86, 102, 118, 134, 150, 166, 182, 198, 214, 230, 246, 262, 278, 286, and 294, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 12, 28, 44, 60, 76, 92, 108, 124, 140, 156, 172, 188, 204, 220, 236, 252, 268, and 300, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 14, 30, 46, 62, 78, 94, 110, 126, 142, 158, 174, 190, 206, 222, 238, 254, 270, and 302, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (v) binds to Bet v 1 with a K_D equal to or less than 10^{-8} and in a range from about 10^{-8} to about 10^{-11}; (vi) demonstrates efficacy in at least one animal model of anaphylaxis or inflammation; or (vii)

competes with a reference antibody for binding to natural Bet v 1, Betula pendula birch BPE, Betula nigra BPE, or Betula populifolia BPE.

[0070] In one embodiment, a "reference antibody" may include, for example, antibodies having a combination of heavy chain and light chain amino acid sequence pairs selected from the group consisting of 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/266, 282/266, and 290/298.

[0071] Also described are antibodies having a modified glycosylation pattern. In some applications, modification to remove undesirable glycosylation sites may be useful, or e.g., removal of a fucose moiety to increase antibody dependent cellular cytotoxicity (ADCC) function (see Shield *et al*., 2002, *JBC* 277: 26733). In other applications, modification of galactosylation can be made in order to modify complement dependent cytotoxicity (CDC).

[0072] Also described is an isolated antibody or antigen-binding fragment thereof that competes for specific binding to natural Bet v 1, Betula pendula birch BPE, Betula nigra BPE, or Betula populifolia BPE with an antibody or antigen-binding fragment comprising the complementarity determining regions (CDRs) of a heavy chain variable region (HCVR), wherein the HCVR has an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 282, and 290; and the CDRs of a light chain variable region (LCVR), wherein the LCVR has an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, and 298.

[0073] One embodiment provides an isolated antibody or antigen-binding fragment thereof that competes for specific binding to natural Bet v 1, Betula pendula birch BPE, Betula nigra BPE, or Betula populifolia BPE with an antibody or antigen-binding fragment comprising the complementarity determining regions (CDRs) of a heavy chain variable region (HCVR), wherein the HCVR has an amino acid sequence selected from the group consisting of SEQ ID NOs: 114, 146, 98, and 290; and the CDRs of a light chain variable region (LCVR), wherein the LCVR has an amino acid sequence selected from the group consisting of SEQ ID NOs: 122, 154, 106, and 298.

[0074] In a related embodiment, described is an isolated antibody or antigen-binding fragment thereof that competes for specific binding to natural Bet v 1, Betula pendula birch BPE, Betula nigra BPE, or Betula populifolia BPE with an antibody or antigen-binding fragment comprising the heavy and light chain CDRs contained within heavy and light chain sequence pairs selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58,

66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/266, 282/266, and 290/298.

[0075] Also described is an isolated antibody or antigen-binding fragment thereof that binds the same epitope on Bet v 1 as an antibody or antigen-binding fragment comprising the complementarity determining regions (CDRs) of a heavy chain variable region (HCVR), wherein the HCVR has an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 282, and 290; and the CDRs of a light chain variable region (LCVR), wherein the LCVR has an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, and 298.

[0076] One embodiment provides an isolated antibody or antigen-binding fragment thereof that binds the same epitope on Bet v 1 as an antibody or antigen-binding fragment comprising the complementarity determining regions (CDRs) of a heavy chain variable region (HCVR), wherein the HCVR has an amino acid sequence selected from the group consisting of SEQ ID NOs: 114, 146, 98, and 290; and the CDRs of a light chain variable region (LCVR), wherein the LCVR has an amino acid sequence selected from the group consisting of SEQ ID NOs: 122, 154, 106, and 298.

[0077] In a related embodiment, provided herein is an isolated antibody or antigen-binding fragment thereof that binds the same epitope on Bet v 1 as an antibody or antigen-binding fragment comprising the heavy and light chain CDRs contained within heavy and light chain sequence pairs selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/266, 282/266, and 290/298.

[0078] Also described are nucleic acid molecules encoding Bet v 1 antibodies or fragments thereof. Recombinant expression vectors carrying such nucleic acids, and host cells into which such vectors have been introduced, are also contemplated herein, as are methods of producing the antibodies by culturing the host cells under conditions permitting production of the antibodies, and recovering the antibodies produced.

[0079] In one embodiment, described are nucleic acid molecules encoding a human monoclonal antibody or fragment thereof that binds to natural Bet v 1, Betula pendula BPE, Betula nigra BPE, or Betula populifolia BPE.

[0080] In one embodiment, described is an antibody or fragment thereof comprising a HCVR encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 1, 17, 33, 49, 65, 81, 97, 113, 129, 145, 161, 177, 193, 209, 225, 241, 257, 273, 281, and

289, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof.

[0081] In one embodiment, the HCVR is encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 113, 145, 257, and 289.

[0082] In one embodiment, the antibody or fragment thereof further comprises a LCVR encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 9, 25, 41, 57, 73, 89, 105, 121, 137, 153, 169, 185, 201, 217, 233, 249, 265, and 297, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof.

[0083] In one embodiment, the LCVR is encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 121, 153, 265, and 297.

[0084] In one embodiment, described is an antibody or antigen-binding fragment of an antibody comprising a HCDR3 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 7, 23, 39, 55, 71, 87, 103, 119, 135, 151, 167, 183, 199, 215, 231, 247, 263, 279, 287, and 295, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR3 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 15, 31, 47, 63, 79, 95, 111, 127, 143, 159, 175, 191, 207, 223, 239, 255, 271, and 303, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0085] In one embodiment, described is an antibody or fragment thereof further comprising a HCDR1 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 3, 19, 35, 51, 67, 83, 99, 115, 131, 147, 163, 179, 195, 211, 227, 243, 259, 275, 283, and 291, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a HCDR2 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 5, 21, 37, 53, 69, 85, 101, 117, 133, 149, 165, 181, 197, 213, 229, 245, 261, 277, 285, and 293, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a LCDR1 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 11, 27, 43, 59, 75, 91, 107, 123, 139, 155, 171, 187, 203, 219, 235, 251, 267, and 299, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR2 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 13, 29, 45, 61, 77, 93, 109, 125, 141, 157, 173, 189, 205, 221, 237, 253, 269, and 301, or a substantially

similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0086] Also described is a pharmaceutical composition comprising a therapeutically effective amount of one or more isolated human antibodies or antigen-binding fragments thereof that bind natural Bet v 1, Betula pendula birch BPE, Betula nigra BPE, or Betula populifolia BPE, together with one or more pharmaceutically acceptable excipients.

[0087] In one embodiment, the pharmaceutical composition comprises a therapeutically effective amount of two or more isolated human antibodies or antigen-binding fragments thereof that bind Bet v 1 together with one or more pharmaceutically acceptable excipients.

[0088] In one embodiment, the pharmaceutical composition comprises:

a) a first isolated human monoclonal antibody or antigen-binding fragment thereof that binds Bet v 1, which comprises a HCVR having an amino acid sequence as set forth in SEQ ID NO: 146; and a LCVR having an amino acid sequence as set forth in SEQ ID NO: 154;

b) a second isolated human monoclonal antibody or antigen-binding fragment thereof that binds Bet v 1, which comprises a HCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs: 114, 98, and 290; and a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs: 122, 106, and 298; and

c) one or more pharmaceutically acceptable excipients.

[0089] In one embodiment, the pharmaceutical composition comprises:

a) a first isolated human monoclonal antibody or antigen-binding fragment thereof that binds Bet v 1, which comprises a HCVR having an amino acid sequence as set forth in SEQ ID NO: 290; and a LCVR having an amino acid sequence as set forth in SEQ ID NO: 298;

b) a second isolated human monoclonal antibody or antigen-binding fragment thereof that binds Bet v 1, which comprises a HCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs: 114, 146, and 98; and a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs: 122, 154, and 106; and

c) one or more pharmaceutically acceptable excipients.

[0090] In one embodiment, the pharmaceutical composition comprises:

a) a first isolated human monoclonal antibody or antigen-binding fragment thereof that binds Bet v 1, which comprises a HCVR having an amino acid sequence as set forth in

SEQ ID NO: 146; and a LCVR having an amino acid sequence as set forth in SEQ ID NO: 154;

b) a second isolated human monoclonal antibody or antigen-binding fragment thereof that binds Bet v 1, which comprises a HCVR having an amino acid sequence as set forth in SEQ ID NOs: 290; and a LCVR having an amino acid sequence as set forth in SEQ ID NOs: 298; and

c) one or more pharmaceutically acceptable excipients.

[0091] In one embodiment, the pharmaceutical composition comprises:

a) a first isolated human monoclonal antibody or antigen-binding fragment thereof comprising a HCVR having an amino acid sequence of SEQ ID NO: 146 and a LCVR having an amino acid sequence of SEQ ID NO: 154;

b) a second isolated human monoclonal antibody or antigen-binding fragment thereof comprising a HCVR having an amino acid sequence of SEQ ID NO: 290 and a LCVR having an amino acid sequence of SEQ ID NO: 298;

c) one or more further isolated human monoclonal antibodies or antigen-binding fragments comprising a HCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs: 114 and 98 and a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs: 122 and 106; and

d) one or more pharmaceutically acceptable excipients.

[0092] In one embodiment, the pharmaceutical composition comprises:

a first isolated human monoclonal antibody or antigen-binding fragment thereof that binds Bet v 1, comprising a HCVR/LCVR amino acid sequence pair consisting of SEQ ID NOs: 146/154;

a second isolated human monoclonal antibody or antigen-binding fragment thereof that binds Bet v 1, comprising a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 114/122, 98/106, and 290/298; and

one or more pharmaceutically acceptable excipients.

[0093] In one embodiment, the pharmaceutical composition comprises:

a first isolated human monoclonal antibody or antigen-binding fragment thereof that binds to Bet v 1, comprising a HCVR/LCVR amino acid sequence pair consisting of SEQ ID NOs: 146/154;

a second isolated human monoclonal antibody or antigen-binding fragment thereof that binds to Bet v 1, comprising a HCVR/LCVR amino acid sequence pair consisting of SEQ ID NOs: 290/298; and

one or more pharmaceutically acceptable excipients.

[0094] In one embodiment, the pharmaceutical composition comprises two or more isolated human monoclonal antibodies or antigen-binding fragments thereof that bind to Bet v 1, comprising HCVR/LCVR amino acid sequence pairs selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/266, 282/266, and 290/298; and one or more pharmaceutically acceptable excipients.

[0095] In one embodiment, the pharmaceutical composition comprises three or more isolated human monoclonal antibodies or antigen-binding fragments thereof that bind to Bet v 1, comprising HCVR/LCVR amino acid sequence pairs selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/266, 282/266, and 290/298; and one or more pharmaceutically acceptable excipients.

[0096] In one embodiment, the pharmaceutical composition comprises four isolated human monoclonal antibodies that bind to Bet v 1, or antigen-binding fragments thereof, wherein the human antibodies or antigen-binding fragments thereof comprise the HCVR/LCVR amino acid sequence pairs of SEQ ID NOs: 114/122, 146/154, 98/106, and 290/298; and one or more pharmaceutically acceptable excipients.

[0097] In one embodiment, the pharmaceutical composition comprises the antibody designated H4H16992P having the HCVR/LCVR amino acid sequence pair of SEQ ID NOs: 146/154; the antibody designated H4H17082P2 having the HCVR/LCVR amino acid sequence pair of SEQ ID NOs: 290/298; and the antibody designated H4H17038P2 having the HCVR/LCVR amino acid sequence pair of SEQ ID NOs: 98/106.

[0098] In one embodiment, the pharmaceutical composition comprises the antibody designated H4H16992P having the HCVR/LCVR amino acid sequence pair of SEQ ID NOs: 146/154; the antibody designated H4H17082P2 having the HCVR/LCVR amino acid sequence pair of SEQ ID NOs: 290/298; the antibody designated H4H17038P2 having the HCVR/LCVR amino acid sequence pair of SEQ ID NOs: 98/106; and the antibody designated H4H16987P having the HCVR/LCVR amino acid sequence pair of SEQ ID NOs: 114/122.

[0099] In one embodiment, the pharmaceutical composition comprises a therapeutically effective amount of a first isolated human monoclonal antibody or an antigen-binding fragment thereof that binds to Bet v 1, wherein the first antibody or fragment thereof interacts with amino acid residues ranging from about position 23 to about position 44 of

SEQ ID NO: 306, and a second isolated human monoclonal antibody or antigen-binding fragment thereof that binds to Bet v 1, wherein the second antibody or fragment thereof interacts with amino acid residues ranging from about position 44 to about position 70 of SEQ ID NO: 306, together with one or more pharmaceutically acceptable excipients.

[00100] In one embodiment, the pharmaceutical composition comprises a therapeutically effective amount of a first isolated human monoclonal antibody or an antigen-binding fragment thereof that binds to Bet v 1, together with one or more pharmaceutically acceptable excipients, wherein the first antibody or fragment thereof interacts with amino acid residues ranging from about position 23 to about position 43 of SEQ ID NO: 306, and a second isolated human monoclonal antibody or antigen-binding fragment thereof that binds to Bet v 1, wherein the second antibody or fragment thereof interacts with amino acid residues ranging from about position 44 to about position 56 of SEQ ID NO: 306.

[00101] In one embodiment, the pharmaceutical composition comprises a therapeutically effective amount of a first isolated human monoclonal antibody or an antigen-binding fragment thereof that binds to Bet v 1, together with one or more pharmaceutically acceptable excipients, wherein the first antibody or fragment thereof interacts with the amino acid sequence of SEQ ID NO: 307, and a second isolated human monoclonal antibody or antigen-binding fragment thereof that binds to Bet v 1, wherein the second antibody or fragment thereof interacts with the amino acid sequence of SEQ ID NO: 308, 309, 310, 311 or 315.

[00102] In one embodiment, the pharmaceutical composition comprises a therapeutically effective amount of a first isolated human monoclonal antibody or an antigen-binding fragment thereof that binds to Bet v 1, and one or more further isolated human monoclonal antibodies, or antigen-binding fragments thereof that bind to Bet v 1, together with one or more pharmaceutically acceptable excipients, wherein the first antibody or fragment thereof interacts with at least one amino acid sequence selected from group consisting of amino acid residues ranging from about position 23 to about position 43 of SEQ ID NO: 306; amino acid residues ranging from about position 44 to about 56 of SEQ ID NO: 306; amino acid residues ranging from about 2 to about 19 of SEQ ID NO: 306; amino acid residues ranging from about 57 to about 70 of SEQ ID NO: 306; and amino acid residues ranging from about 81 to 89 or about 81 to about 96 of SEQ ID NO: 306.

[00103] In one embodiment, the one or more further isolated human monoclonal antibodies or fragments thereof interacts with at least one amino acid sequence selected from the group consisting of amino acid residues ranging from about position 23 to about position

43 of SEQ ID NO: 306; amino acid residues ranging from about position 44 to about 56 of SEQ ID NO: 306; amino acid residues ranging from about 2 to about 19 of SEQ ID NO: 306; amino acid residues ranging from about 57 to about 70 of SEQ ID NO: 306; and amino acid residues ranging from about 81 to 89 or about 81 to about 96 of SEQ ID NO: 306, wherein at least one of the one or more further isolated human monoclonal antibodies interacts with a different amino acid sequence than the first isolated human monoclonal antibody.

[00104] In one embodiment, the pharmaceutical composition comprises a therapeutically effective amount of a first isolated human monoclonal antibody or an antigen-binding fragment thereof that binds to Bet v 1, and one or more further isolated human monoclonal antibodies, or antigen-binding fragments thereof that bind to Bet v 1, together with one or more pharmaceutically acceptable excipients, wherein the first antibody or fragment thereof interacts with the amino acid sequence of SEQ ID NO: 307 and wherein the one or more further antibodies or fragments thereof interact with an amino acid sequence selected from the group consisting of SEQ ID NOs: 308, 309, 310, 311, and 315.

[00105] In one embodiment, the pharmaceutical composition comprises a therapeutically effective amount of at least two isolated human monoclonal antibodies or antigen-binding fragments thereof that bind to natural Bet v 1 or BPE, together with one or more pharmaceutically acceptable excipients, wherein the at least two antibodies do not compete for binding to natural Bet v 1 or BPE. In some aspects, the antibodies or antigen-binding fragments thereof are the Bet v 1 antibodies H4H16992P and H4H17082P2 comprising the HCVR/LCVR amino acid sequence pairs of SEQ ID NOs: 146/154 and 290/298, respectively.

[00106] In one embodiment, the pharmaceutical composition comprises a therapeutically effective amount of at least three isolated human monoclonal antibodies or antigen-binding fragments thereof that bind to natural Bet v 1 or BPE, together with one or more pharmaceutically acceptable excipients, wherein the at least three antibodies do not compete for binding to natural Bet v 1 or BPE. In some aspects, the antibodies or antigen-binding fragments thereof are the Bet v 1 antibodies H4H16992P, H4H17082P2, and H4H17038P2 comprising the HCVR/LCVR amino acid sequence pairs of SEQ ID NOs: 146/154, 290/298, and 98/106, respectively.

[00107] In one embodiment, the pharmaceutical composition comprises a therapeutically effective amount of at least four isolated human monoclonal antibodies or antigen-binding fragments thereof that bind to natural Bet v 1 or BPE, together with one or more pharmaceutically acceptable excipients, wherein the at least four antibodies do not

compete for binding to natural Bet v 1 or BPE. In some aspects, the antibodies or antigen-binding fragments thereof are the Bet v 1 antibodies H4H16992P, H4H17082P2, H4H17038P2, and H4H16987P comprising the HCVR/LCVR amino acid sequence pairs of SEQ ID NOs: 146/154, 290/298, 98/106, and 114/122, respectively.

[00108] In one embodiment, the pharmaceutical composition comprises a therapeutically effective amount of an isolated human monoclonal antibody or antigen-binding fragment thereof that binds to Bet v 1, together with one or more pharmaceutically acceptable excipients, wherein the antibody or antigen-binding fragment thereof cross-reacts with one or more allergens selected from the group consisting of Aln g1, Cor a1, Car b1, Que a1, Api g2, Api g1, Dau c1, Mal d1, Ost c1, Fag s1, and Cas s1. In some embodiments, the antibody or antigen-binding fragment thereof cross-reacts with one or more allergens selected from the group consisting of Aln g1, Mal d1, Api g1, Car b1, and Cor a1.

[00109] In one embodiment, the invention features a composition, which is a combination of a therapeutically effective amount of one or more anti-Bet v 1 antibodies or antigen-binding fragments thereof of the invention, and a therapeutically effective amount of a second therapeutic agent, together with one or more pharmaceutically acceptable excipients.

[00110] The second therapeutic agent may be a small molecule drug, a protein/polypeptide, an antibody, a nucleic acid molecule, such as an anti-sense molecule, or a siRNA. The second therapeutic agent may be synthetic or naturally derived.

[00111] The second therapeutic agent may be any agent that is advantageously combined with an antibody or fragment thereof of the invention, for example, a second antibody other than those described herein that is capable of blocking the binding of Bet v 1 to IgE present on mast cells or basophils. A second therapeutic agent may also be any agent that is used as standard of care in treating an allergic response to any allergen. Such second therapeutic agent may be an antihistamine, epinephrine, a decongestant, a corticosteroid, or a peptide vaccine.

[00112] In certain embodiments, the second therapeutic agent may be an agent that helps to counteract or reduce any possible side effect(s) associated with the antibody or antigen-binding fragment of an antibody of the invention, if such side effect(s) should occur.

[00113] It will also be appreciated that the antibodies and pharmaceutically acceptable compositions of the present invention can be employed in combination therapies, that is, the antibodies and pharmaceutically acceptable compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures,

including, for example in combination with an allergen-specific immunotherapy (SIT) regimen where the antibodies are administered before or during SIT. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, an antibody may be administered concurrently with another agent used to treat the same disorder), or they may achieve different effects (*e.g.,* control of any adverse effects). As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular disease, or condition, are appropriate for the disease, or condition, being treated.

[00114] When multiple therapeutics are co-administered, dosages may be adjusted accordingly, as is recognized in the pertinent art.

[00115] Also described is a method for treating a patient who demonstrates a sensitivity to, or an allergic reaction against, a Fagales protein, a Fagales related allergen, birch pollen or an extract thereof, or Bet v 1 protein, or for treating at least one symptom or complication associated with a sensitivity to, or allergic reaction against a Fagales protein, a Fagales related allergen, birch pollen or an extract thereof, or Bet v 1 protein, comprising administering an effective amount of one or more isolated human monoclonal antibodies or antigen-binding fragments thereof that bind to natural Bet v 1, Betula pendula BPE, Betula nigra BPE, or Betula populifolia BPE, or a pharmaceutical composition comprising an effective amount of one or more isolated human monoclonal antibodies or fragments thereof that bind to natural Bet v 1, Betula pendula BPE, Betula nigra BPE, or Betula populifolia BPE, to a patient in need thereof, wherein the sensitivity to, or an allergic reaction against, a Fagales protein, a Fagales related allergen, birch pollen or an extract thereof, or Bet v 1 protein is either prevented, or lessened in severity and/or duration, or at least one symptom or complication associated with the sensitivity to, or allergic reaction against, a Fagales protein, a Fagales related allergen, birch pollen or an extract thereof, or Bet v 1 protein is prevented, or ameliorated, or that the frequency and/or duration of, or the severity of the sensitivity to or allergic reaction against, a Fagales protein, a Fagales related-protein, birch pollen or an extract thereof, or Bet v 1 protein is reduced following administration of one or more of the isolated human monoclonal antibodies or fragments thereof that bind to natural Bet v 1, Betula pendula BPE, Betula nigra BPE, or Betula populifolia BPE, or following administration of a composition comprising any one or more of the foregoing antibodies.

[00116] In some embodiments, the birch pollen extract is selected from the group consisting of natural Bet v 1, Betula pendula BPE, Betula nigra BPE, and Betula populifolia BPE.

[00117] In some embodiments, the treatment results in a reduction in allergic rhinitis, allergic conjunctivitis, allergic asthma, or an anaphylactic response following exposure of the patient to a Fagales protein, a Fagales related allergen, birch pollen or an extract thereof, or Bet v 1 protein.

[00118] In some embodiments, the method further comprises administering an effective amount of a second therapeutic agent useful for diminishing an allergic reaction to a Fagales protein, a Fagales related allergen, birch pollen or an extract thereof, or Bet v 1 protein. The second therapeutic agent can be selected from the group consisting of a corticosteroid, a bronchial dilator, an antihistamine, epinephrine, a decongestant, another different antibody to Bet v 1 and a peptide vaccine.

[00119] In some embodiments, the method further comprises treating the patient with an allergen-specific immunotherapy (SIT) regimen just after or concurrent with the antibodies or fragments thereof or the pharmaceutical composition comprising the antibodies.

[00120] In one embodiment, the invention provides a method for treating a Fagales allergic patient who demonstrates a sensitivity to, or an allergic reaction against, one or more Fagales allergens, or Fagales related allergens, or for treating at least one symptom or complication associated with a sensitivity to, or allergic reaction against one or more Fagales allergens, or Fagales related allergens, comprising administering an effective amount of one or more isolated human monoclonal antibodies or antigen-binding fragments thereof that bind Bet v 1, or a pharmaceutical composition comprising an effective amount of one or more isolated human monoclonal antibodies or fragments thereof that bind to Bet v 1, to a patient in need thereof, wherein the sensitivity to, or an allergic reaction against, a Fagales allergen, or Fagales related allergen, is either prevented, or lessened in severity and/or duration, or at least one symptom or complication associated with the sensitivity to, or allergic reaction against, a Fagales allergen, or Fagales related allergen, is prevented, or ameliorated, or that the frequency and/or duration of, or the severity of the sensitivity to or allergic reaction against, a Fagales allergen, or Fagales related allergen, is reduced following administration of one or more of the isolated human monoclonal antibodies or fragments thereof that bind Bet v 1, or following administration of a composition comprising any one or more of the foregoing antibodies.

[00121] In some embodiments, the one or more Fagales allergens is selected from the group consisting of Bet v 1, Aln g1, Cor a1, Car b1, and Que a1.

[00122] In one embodiment, described is a pharmaceutical composition comprising one or more of the antibodies described herein that bind natural Bet v 1, Betula pendula BPE, Betula nigra BPE, and Betula populifolia BPE for use in treating a patient who demonstrates a sensitivity to, or an allergic reaction against, a Fagales protein, birch pollen or an extract thereof, or Bet v 1 protein, or for treating at least one symptom or complication associated with a sensitivity to, or allergic reaction against, a Fagales protein, birch pollen or an extract thereof, or Bet v 1 protein, wherein the sensitivity to, or an allergic reaction against, a Fagales protein, birch pollen or an extract thereof, or Bet v 1 protein is either prevented, or lessened in severity and/or duration, or at least one symptom or complication associated with the sensitivity to, or allergic reaction against, a Fagales protein, birch pollen or an extract thereof, or Bet v 1 protein is prevented, or ameliorated, or that the frequency and/or duration of, or the severity of the sensitivity to or allergic reaction against, a Fagales protein, birch pollen or an extract thereof, or Bet v 1 protein is reduced.

[00123] In one embodiment, the invention provides for use of a pharmaceutical composition comprising one or more of the antibodies of the invention that binds to Bet v 1 in the manufacture of a medicament for use in treating a patient who demonstrates a sensitivity to, or an allergic reaction against, birch pollen or an extract thereof, or to Bet v 1 protein, or for treating at least one symptom or complication associated with a sensitivity to, or allergic reaction against, birch pollen or an extract thereof, or to Bet v 1 protein, wherein the sensitivity to, or an allergic reaction against, birch pollen or an extract thereof, or to Bet v 1 protein is either prevented, or lessened in severity and/or duration, or at least one symptom or complication associated with the sensitivity to, or allergic reaction against, birch pollen or an extract thereof, or to Bet v 1 protein is prevented, or ameliorated, or that the frequency and/or duration of, or the severity of the sensitivity to or allergic reaction against, birch pollen or an extract thereof, or to Bet v 1 protein is reduced.

[00124] In one embodiment, described is a use of a pharmaceutical composition as described above, wherein the composition is administered in combination with a second therapeutic agent useful for diminishing an allergic reaction to a Fagales protein, birch pollen or an extract thereof, or Bet v 1 protein. In one embodiment, described is a use of the pharmaceutical composition as described above, wherein the second therapeutic agent is selected from a corticosteroid, a bronchial dilator, an antihistamine, epinephrine, a decongestant, another different antibody to Bet v 1 and a peptide vaccine.

[00125] In certain embodiments, the antibodies of the invention that bind to Bet v 1 may be capable of reducing, minimizing, or preventing at least one symptom in a patient sensitive to birch pollen or Bet v 1, such as sneezing, congestion, nasal blockage, coughing, wheezing, bronchoconstriction, rhinitis, or conjunctivitis.

[00126] In one embodiment, the antibodies of the invention that bind to Bet v 1, or a composition comprising one or more antibodies of the invention may be used to prevent more serious *in vivo* complications associated with an allergy to Bet v 1, including asthmatic responses, anaphylactic shock, or even death resulting from anaphylaxis.

[00127] In one embodiment, the pharmaceutical composition is administered to the patient in combination with a second therapeutic agent.

[00128] In another embodiment, the second therapeutic agent is selected from the group consisting of an antihistamine, epinephrine, a decongestant, a corticosteroid, another different antibody to Bet v 1, a peptide vaccine and any other palliative therapy useful for reducing the severity of the allergic reaction or for ameliorating at least one symptom associated with the allergic reaction.

[00129] In yet another embodiment, the pharmaceutical composition is administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures, including, for example, administered prior to or concurrently with an allergen-specific immunotherapy (SIT) regimen. In some aspects, use of a SIT regimen together with the antibodies provided herein provides a synergistic effect.

[00130] In one embodiment, a method is provided for enhancing the efficacy and/or safety of an allergen-specific immunotherapy (SIT) regimen, the method comprising administering an effective amount of one or more isolated human monoclonal antibodies or antigen-binding fragments thereof, as provided herein, or a pharmaceutical composition comprising an effective amount of one or more isolated human monoclonal antibodies or fragments thereof, to a patient in need thereof just prior to or concurrent with the SIT regimen, wherein the severity of an allergic reaction to the SIT regimen is mitigated. In some embodiments, the SIT regimen comprises an up-dosing phase followed by a maintenance phase. In some embodiments, the SIT regimen is a rush SIT regimen.

[00131] Also described is a method is provided for preventing or reducing mast cell degranulation associated with Fagales protein, Fagales related allergen, birch pollen or birch pollen extract, or Bet v 1 sensitization, the method comprising administering a pharmaceutical composition described herein to a patient in need thereof.

[00132] In some embodiments, the BPE is selected from the group consisting of natural Bet v 1, Betula pendula BPE, Betula nigra BPE, and Betula populifolia BPE.

[00133] Other embodiments will become apparent from a review of the ensuing detailed description.

BRIEF DESCRIPTION OF THE FIGURES

[00134] Figure 1 provides H/D exchange/MS epitope mapping for interaction of H4H16992P with Bet v 1.

[00135] Figure 2 provides H/D exchange/MS epitope mapping for interaction of H4H17082P with Bet v 1.

[00136] Figure 3 provides H/D exchange/MS epitope mapping for interaction of H4H17038P2with Bet v 1.

[00137] Figure 4 provides H/D exchange/MS epitope mapping for interaction of H4H16987P with Bet v 1.

[00138] Figure 5 provides H/D exchange/MS epitope mapping for interaction of H4H16992P, H4H17082P, H4H17038P2 and H4H16987P with Bet v 1.

[00139] Figure 6 is a diagram of the protocol used to determine the effectiveness of the antibody combinations in blocking mast cell degranulation induced by Bet v 1 in a humanized mouse PCA model.

[00140] Figure 7 depicts ability of anti-Bet v 1 antibody combinations to block mast cell degranulation in a humanized mouse PCA model using IgE containing sera obtained from three Bet v 1 sensitive donors.

[00141] Figure 8 depicts two graphs, the first providing representative data demonstrating anti-Bet v 1 antibody combinations that block basophil activation in PBMCs obtained from one birch allergic donor. The bar graph provides data depicting percent blocking of basophil activation in PBMCs obtained from multiple donors by the anti-Bet v 1 antibody combinations relative to each antibody alone.

DESCRIPTION

[00142] Before the present compositions and methods are described, it is to be understood that this invention is not limited to particular compositions and methods, and experimental conditions described, as such methods, compositions, and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing

particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

[00143] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. As used herein, the term "about," when used in reference to a particular recited numerical value, means that the value may vary from the recited value by no more than 1%. For example, as used herein, the expression "about 100" includes 99 and 101 and all values in between (*e.g.*, 99.1, 99.2, 99.3, 99.4, etc.).

[00144] Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, preferred methods and materials are now described.

Definitions

[00145] The term "Bet v 1" as used herein, refers to at least one Bet v 1 protein, either in natural/native form, or recombinantly produced. The Bet v 1 protein comprises the amino acid sequence of SEQ ID NO: 306 and the nucleic acid sequence of SEQ ID NO: 305. The natural Bet v 1 protein is approximately 17 kD and exists as a 7 stranded anti-parallel β-sheet (β1–β7), two short α-helices (α1 and α2) connecting β1 and β2, a long C-terminal α-helix (α3), and the glycine-rich loop motif between β2 and β3 (Kofler *et al.* (2012) *J. Mol. Biol.* 422(1): 109-123). A recombinantly produced mutant Bet v 1, SEQ ID NO: 312, comprises G2-N160 of Uniprot P15494 with a S85A substitution and contains a Myc-Myc-hexahistidine tag. The Bet v 1 amino acid sequence from Uniprot: P15494, i.e. SEQ ID NO: 314, can also refer to Bet v 1.

[00146] "Bet v 1" is a polypeptide comprising, or alternatively, consisting of, an amino acid sequence of SEQ ID NO: 306 or SEQ ID NO: 314, or a homologous sequence thereof. The phrase "homologous sequence of SEQ ID NO: 306 or SEQ ID NO: 314", as used herein, refers to a polypeptide that has an identity to SEQ ID NO: 306 or SEQ ID NO: 314 which is greater than 70%, preferably greater than 80%, more preferably greater than 90%, and even more preferably greater than 95%.

[00147] The term "Bet v 1 fragment" as used herein, refers to a polypeptide comprising or alternatively consisting of, at least one antigenic site of Bet v 1. In one embodiment, the term "Bet v 1 fragment" as used herein, refers to a polypeptide comprising or alternatively consisting of at least two antigenic sites of Bet v 1. In one embodiment, the antigenic sites are covalently linked. In one embodiment, the antigenic sites are linked by at

least one peptide bond. In one embodiment, the two antigenic sites are linked by at least one peptide bond and a spacer between the antigenic sites. In one embodiment, the at least two antigenic sites comprise amino acid sequences 23-44 and 44-56 of Uniprot P15494. In one embodiment, the at least two antigenic sites comprise an amino acid sequence within any of SEQ ID NOs: 306, 307, 308, 309, 310, 311, and 315. In one embodiment, any of the Bet v 1 fragments are capable of inducing the production of antibodies *in vivo* that specifically bind to naturally occurring Bet v 1, or to recombinantly produced Bet v 1.

[00148] The term "antibody", as used herein, means any antigen-binding molecule or molecular complex comprising at least one complementarity determining region (CDR) that specifically binds to or interacts with a particular antigen (*e.g.*, Bet v 1). The term "antibody", as used herein, is intended to refer to immunoglobulin molecules comprised of four polypeptide chains, two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds (*i.e.*, "full antibody molecules"), as well as multimers thereof (*e.g.* IgM) or antigen-binding fragments thereof. Each heavy chain is comprised of a heavy chain variable region ("HCVR" or "V_H") and a heavy chain constant region (comprised of domains C_H1, C_H2 and C_H3). Each light chain is comprised of a light chain variable region ("LCVR or "V_L") and a light chain constant region (C_L). The V_H and V_L regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each V_H and V_L is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. In certain embodiments of the invention, the FRs of the antibody (or antigen binding fragment thereof) may be identical to the human germline sequences, or may be naturally or artificially modified. An amino acid consensus sequence may be defined based on a side-by-side analysis of two or more CDRs.

[00149] Substitution of one or more CDR residues or omission of one or more CDRs is also possible. Antibodies have been described in the scientific literature in which one or two CDRs can be dispensed with for binding. Padlan *et al.* (1995, *FASEB J.* 9:133-139) analyzed the contact regions between antibodies and their antigens, based on published crystal structures, and concluded that only about one fifth to one third of CDR residues actually contact the antigen. Padlan also found many antibodies in which one or two CDRs had no amino acids in contact with an antigen (see also, Vajdos *et al.,* 2002, *J Mol Biol* 320:415-428).

[00150] CDR residues not contacting antigen can be identified based on previous studies (for example residues H60-H65 in CDRH2 are often not required), from regions of Kabat CDRs lying outside Chothia CDRs, by molecular modeling and/or empirically. If a CDR or residue(s) thereof is omitted, it is usually substituted with an amino acid occupying the corresponding position in another human antibody sequence or a consensus of such sequences. Positions for substitution within CDRs and amino acids to substitute can also be selected empirically. Empirical substitutions can be conservative or non-conservative substitutions.

[00151] The fully human monoclonal antibodies that specifically bind to Bet v 1, as disclosed herein, may comprise one or more amino acid substitutions, insertions and/or deletions in the framework and/or CDR regions of the heavy and light chain variable domains as compared to the corresponding germline sequences. Such mutations can be readily ascertained by comparing the amino acid sequences disclosed herein to germline sequences available from, for example, public antibody sequence databases. The present invention includes antibodies, and antigen-binding fragments thereof, which are derived from any of the amino acid sequences disclosed herein, wherein one or more amino acids within one or more framework and/or CDR regions are mutated to the corresponding residue(s) of the germline sequence from which the antibody was derived, or to the corresponding residue(s) of another human germline sequence, or to a conservative amino acid substitution of the corresponding germline residue(s) (such sequence changes are referred to herein collectively as "germline mutations"). A person of ordinary skill in the art, starting with the heavy and light chain variable region sequences disclosed herein, can easily produce numerous antibodies and antigen-binding fragments which comprise one or more individual germline mutations or combinations thereof. In certain embodiments, all of the framework and/or CDR residues within the V_H and/or V_L domains are mutated back to the residues found in the original germline sequence from which the antibody was derived. In other embodiments, only certain residues are mutated back to the original germline sequence, *e.g.*, only the mutated residues found within the first 8 amino acids of FR1 or within the last 8 amino acids of FR4, or only the mutated residues found within CDR1, CDR2 or CDR3. In other embodiments, one or more of the framework and/or CDR residue(s) are mutated to the corresponding residue(s) of a different germline sequence (*i.e.*, a germline sequence that is different from the germline sequence from which the antibody was originally derived).

[00152] Furthermore, the antibodies described may contain any combination of two or more germline mutations within the framework and/or CDR regions, *e.g.*, wherein certain

individual residues are mutated to the corresponding residue of a particular germline sequence while certain other residues that differ from the original germline sequence are maintained or are mutated to the corresponding residue of a different germline sequence. Once obtained, antibodies and antigen-binding fragments that contain one or more germline mutations can be easily tested for one or more desired property such as, improved binding specificity, increased binding affinity, improved or enhanced antagonistic or agonistic biological properties (as the case may be), reduced immunogenicity, etc. Antibodies and antigen-binding fragments obtained in this general manner are encompassed within the present invention.

[00153] Also described are fully human monoclonal antibodies comprising variants of any of the HCVR, LCVR, and/or CDR amino acid sequences disclosed herein having one or more conservative substitutions. For example, the present invention includes antibodies having HCVR, LCVR, and/or CDR amino acid sequences with, *e.g.*, 10 or fewer, 8 or fewer, 6 or fewer, 4 or fewer, etc. conservative amino acid substitutions relative to any of the HCVR, LCVR, and/or CDR amino acid sequences disclosed herein.

[00154] The term "human antibody", as used herein, is intended to include non-naturally occurring human antibodies. The term includes antibodies that are recombinantly produced in a non-human mammal, or in cells of a non-human mammal. The term is not intended to include antibodies isolated from or generated in a human subject.

[00155] The antibodies of the invention may, in some embodiments, be recombinant and/or non-naturally occurring human antibodies. The term "recombinant human antibody", as used herein, is intended to include all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies expressed using a recombinant expression vector transfected into a host cell (described further below), antibodies isolated from a recombinant, combinatorial human antibody library (described further below), antibodies isolated from an animal (e.g., a mouse) that is transgenic for human immunoglobulin genes (see e.g., Taylor *et al.,* 1992, *Nucl. Acids Res.* 20:6287-6295) or antibodies prepared, expressed, created or isolated by any other means that involves splicing of human immunoglobulin gene sequences to other DNA sequences. In certain embodiments, such recombinant human antibodies are subjected to *in vitro* mutagenesis (or, when an animal transgenic for human Ig sequences is used, *in vivo* somatic mutagenesis) and thus the amino acid sequences of the V_H and V_L regions of the recombinant antibodies are sequences that, while related to human germline V_H and V_L sequences, may not naturally exist within the human antibody germline repertoire *in vivo*.

[00156] Human antibodies can exist in two forms that are associated with hinge heterogeneity. In one form, an immunoglobulin molecule comprises a stable four chain construct of approximately 150-160 kDa in which the dimers are held together by an interchain heavy chain disulfide bond. In a second form, the dimers are not linked via inter-chain disulfide bonds and a molecule of about 75-80 kDa is formed composed of a covalently coupled light and heavy chain (half-antibody). These forms have been extremely difficult to separate, even after affinity purification.

[00157] The frequency of appearance of the second form in various intact IgG isotypes is due to, but not limited to, structural differences associated with the hinge region isotype of the antibody. A single amino acid substitution in the hinge region of the human IgG4 hinge can significantly reduce the appearance of the second form (Angal *et al.,* 1993, *Molecular Immunology* 30:105) to levels typically observed using a human IgG1 hinge. The instant invention encompasses antibodies having one or more mutations in the hinge, C_H2 or C_H3 region, which may be desirable, for example, in production, to improve the yield of the desired antibody form.

[00158] As used herein, the expression "antigen-binding molecule" means a protein, polypeptide or molecular complex comprising or consisting of at least one complementarity determining region (CDR) that alone, or in combination with one or more additional CDRs and/or framework regions (FRs), specifically binds to a particular antigen. In certain embodiments, an antigen-binding molecule is an antibody or a fragment of an antibody, as those terms are defined elsewhere herein.

[00159] The phrase "specifically binds" or "binds specifically to" or the like, means that an antibody or antigen-binding fragment thereof forms a complex with an antigen that is relatively stable under physiologic conditions. Specific binding can be characterized by an equilibrium dissociation constant of at least about $1x10^{-6}$ M or less (*e.g.*, a smaller K_D denotes a tighter binding). Methods for determining whether two molecules specifically bind are well known in the art and include, for example, equilibrium dialysis, surface plasmon resonance, and the like. As described herein, antibodies have been identified by surface plasmon resonance, *e.g.*, BIACORE™, which bind specifically to Bet v 1.

[00160] The phrase "high affinity" antibody refers to those monoclonal antibodies having a binding affinity to Bet v 1, expressed as K_D, of at least 10^{-8} M; preferably 10^{-9} M; more preferably 10^{-10}M, even more preferably 10^{-11} M, even more preferably 10^{-12} M, as measured by surface plasmon resonance, e.g., BIACORE™ or solution-affinity ELISA.

[00161] By the term "slow off rate", "Koff" or "kd" is meant an antibody that dissociates from Bet v 1, with a rate constant of 1 x 10^{-3} s^{-1} or less, preferably 1 x 10^{-4} s^{-1} or less, as determined by surface plasmon resonance, *e.g.*, BIACORE™.

[00162] The terms "antigen-binding portion" of an antibody, "antigen-binding fragment" of an antibody, and the like, as used herein, include any naturally occurring, enzymatically obtainable, synthetic, or genetically engineered polypeptide or glycoprotein that specifically binds an antigen to form a complex. The terms "antigen-binding portion" of an antibody, or "antibody fragment", as used herein, refers to one or more fragments of an antibody that retain the ability to bind to Bet v 1.

[00163] The specific embodiments, antibody or antibody fragments of the invention may be conjugated to a therapeutic moiety ("immunoconjugate"), such as a corticosteroid, a second anti-Bet v 1 antibody, or epinephrine, a vaccine, or any other therapeutic moiety useful for treating an allergic response to Bet v 1.

[00164] The antibodies of the invention may be isolated antibodies. An "isolated antibody," as used herein, means an antibody that has been identified and separated and/or recovered from at least one component of its natural environment. For example, an antibody that has been separated or removed from at least one component of an organism, or from a tissue or cell in which the antibody naturally exists or is naturally produced, is an "isolated antibody" for purposes of the present invention. An isolated antibody also includes an antibody in situ within a recombinant cell. Isolated antibodies are antibodies that have been subjected to at least one purification or isolation step. According to certain embodiments, an isolated antibody may be substantially free of other cellular material and/or chemicals.

[00165] According to certain embodiments, an isolated antibody may be substantially free of other antibodies (Abs) having different antigenic specificities (*e.g.,* an isolated antibody that specifically binds Bet v 1, or a fragment thereof, is substantially free of Abs that specifically bind antigens other than Fagales antigens, or in some aspects, other than Bet v 1.

[00166] A "blocking antibody" or a "neutralizing antibody", as used herein (or an "antibody that neutralizes Bet v 1 activity"), is intended to refer to an antibody, or an antigen binding portion thereof, whose binding to Bet v 1 results in inhibition of at least one biological activity of Bet v 1. For example, an antibody of the invention may aid in preventing the primary allergic response to Bet v 1. Alternatively, an antibody of the invention may demonstrate the ability to prevent a secondary allergic response to Bet v 1, or at least one symptom of an allergic response to Bet v 1, including sneezing, coughing, an asthmatic condition, or an anaphylactic response caused by Bet v 1. This inhibition of the

biological activity of Bet v 1 can be assessed by measuring one or more indicators of Bet v 1 biological activity by one or more of several standard *in vitro* or *in vivo* assays (such as a passive cutaneous anaphylaxis assay, as described herein) or other *in vivo* assays known in the art (for example, other animal models to look at protection from challenge with Bet v 1 following administration of one or more of the antibodies described herein).

[00167] The term "surface plasmon resonance", as used herein, refers to an optical phenomenon that allows for the analysis of real-time biomolecular interactions by detection of alterations in protein concentrations within a biosensor matrix, for example using the BIACORE™ system (Pharmacia Biosensor AB, Uppsala, Sweden and Piscataway, N.J.).

[00168] The term "K_D ", as used herein, is intended to refer to the equilibrium dissociation constant of a particular antibody-antigen interaction.

[00169] The term "epitope" refers to an antigenic determinant that interacts with a specific antigen binding site in the variable region of an antibody molecule known as a paratope. A single antigen may have more than one epitope. Thus, different antibodies may bind to different areas on an antigen and may have different biological effects. The term "epitope" also refers to a site on an antigen to which B and/or T cells respond. It also refers to a region of an antigen that is bound by an antibody. Epitopes may be either linear or conformational. A linear epitope is one produced by adjacent amino acid residues in a polypeptide chain. A conformational epitope is produced by spatially juxtaposed amino acids from different segments of the linear polypeptide chain. In certain embodiments, epitopes may include determinants that are chemically active surface groupings of molecules such as amino acids, sugar side chains, phosphoryl groups, or sulfonyl groups, and, in certain embodiments, may have specific three-dimensional structural characteristics, and/or specific charge characteristics. Epitopes may also be defined as structural or functional. Functional epitopes are generally a subset of the structural epitopes and have those residues that directly contribute to the affinity of the interaction. Epitopes formed from contiguous amino acids are typically retained on exposure to denaturing solvents, whereas epitopes formed by tertiary folding are typically lost on treatment with denaturing solvents. An epitope typically includes at least 3, and more usually, at least 5 or 8-10 amino acids in a unique spatial conformation.

[00170] The term "substantial identity" or "substantially identical," when referring to a nucleic acid or fragment thereof, indicates that, when optimally aligned with appropriate nucleotide insertions or deletions with another nucleic acid (or its complementary strand), there is nucleotide sequence identity in at least about 90%, and more preferably at least about 95%, 96%, 97%, 98% or 99% of the nucleotide bases, as measured by any well-known

algorithm of sequence identity, such as FASTA, BLAST or GAP, as discussed below. A nucleic acid molecule having substantial identity to a reference nucleic acid molecule may, in certain instances, encode a polypeptide having the same or substantially similar amino acid sequence as the polypeptide encoded by the reference nucleic acid molecule.

[00171] As applied to polypeptides, the term "substantial similarity" or "substantially similar" means that two peptide sequences, when optimally aligned, such as by the programs GAP or BESTFIT using default gap weights, share at least 90% sequence identity, even more preferably at least 95%, 98% or 99% sequence identity. Preferably, residue positions, which are not identical, differ by conservative amino acid substitutions. A "conservative amino acid substitution" is one in which an amino acid residue is substituted by another amino acid residue having a side chain (R group) with similar chemical properties (e.g., charge or hydrophobicity). In general, a conservative amino acid substitution will not substantially change the functional properties of a protein. In cases where two or more amino acid sequences differ from each other by conservative substitutions, the percent or degree of similarity may be adjusted upwards to correct for the conservative nature of the substitution. Means for making this adjustment are well known to those of skill in the art. (See, *e.g.*, Pearson, 1994, Methods Mol. Biol. 24: 307-331). Examples of groups of amino acids that have side chains with similar chemical properties include 1) aliphatic side chains: glycine, alanine, valine, leucine and isoleucine; 2) aliphatic-hydroxyl side chains: serine and threonine; 3) amide-containing side chains: asparagine and glutamine; 4) aromatic side chains: phenylalanine, tyrosine, and tryptophan; 5) basic side chains: lysine, arginine, and histidine; 6) acidic side chains: aspartate and glutamate, and 7) sulfur-containing side chains: cysteine and methionine. Preferred conservative amino acids substitution groups are: valine-leucine-isoleucine, phenylalanine-tyrosine, lysine-arginine, alanine-valine, glutamate-aspartate, and asparagine-glutamine. Alternatively, a conservative replacement is any change having a positive value in the PAM250 log-likelihood matrix disclosed in Gonnet *et al.* (1992 *Science* 256: 1443-45). A "moderately conservative" replacement is any change having a nonnegative value in the PAM250 log-likelihood matrix.

[00172] Sequence similarity for polypeptides is typically measured using sequence analysis software. Protein analysis software matches similar sequences using measures of similarity assigned to various substitutions, deletions and other modifications, including conservative amino acid substitutions. For instance, GCG software contains programs such as GAP and BESTFIT which can be used with default parameters to determine sequence homology or sequence identity between closely related polypeptides, such as homologous

polypeptides from different species of organisms or between a wild type protein and a mutein thereof. See, *e.g.,* GCG Version 6.1. Polypeptide sequences also can be compared using FASTA with default or recommended parameters; a program in GCG Version 6.1. FASTA (*e.g.,* FASTA2 and FASTA3) provides alignments and percent sequence identity of the regions of the best overlap between the query and search sequences (Pearson, 2000 *supra*). Another preferred algorithm when comparing a sequence of the invention to a database containing a large number of sequences from different organisms is the computer program BLAST, especially BLASTP or TBLASTN, using default parameters. (See, *e.g.,* Altschul *et al.*, 1990, *J. Mol. Biol.* 215: 403-410 and 1997 *Nucleic Acids Res.* 25:3389-3402).

[00173] By the phrase "therapeutically effective amount" is meant an amount that produces the desired effect for which it is administered. The exact amount will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (see, for example, Lloyd (1999) The Art, Science and Technology of Pharmaceutical Compounding).

[00174] The antibodies of the invention may be used to "desensitize" a Fagales allergic individual. The term to "desensitize" is defined herein as to decrease the allergic-reactivity of a Fagales allergic individual to exposure to a Fagales allergen, such as birch pollen, *e.g.* Bet v 1, Aln g1, Cor a1, Car b1, Que a1, Api g2, Api g1, Dau c1, Mal d1, Ost c1, Fag s1, and/or Cas s1 (to a level less than that which the Fagales allergic individual would otherwise experience), or to a Fagales related allergen. The term "desensitize" is further defined herein as to decrease the allergic-reactivity of an individual to PR-10 proteins including Act c 8 and Act d 8 (kiwi), Ara h 8 (peanut), Pru ar 1 (apricot), Pru av 1 (cherry), Pru p 1 (peach), Pyr c 1 (pear), Gly m 4 (soybean), Vig r 1 (mung bean), Sola I 4 (tomato), Cuc m 3 (melon), Rub i 1 (raspberry), and Fra a 1 (strawberry).

General Description

[00175] Trees belonging to the order of Fagales are the source of spring allergy symptoms, and the major birch allergen, Bet v 1 is responsible for IgE binding in more than 95% of birch pollen allergic patients (Breiteneder, EMBO J. 1989, 8(7):1935-8). Birch is the predominant trigger in 23% of US and 14% of European allergy patients. (DataMonitor report on Allergic Rhinitis, July, 2010). The severity of the symptoms in individuals who demonstrate a sensitivity to birch pollen ranges from a relatively mild rhinitis and conjunctivitis to a potentially life-threatening asthmatic condition. It has been shown that

greater than 60% of patients who are allergic to birch pollen have IgE antibodies to this Bet v 1 (Jarolim et al., Int Arch Allergy Appl Immunol. 1989, 88(1-2):180-2).

[00176] Fagales trees show a distinct geographical distribution where birch and alder are endemic in the northern parts of Europe and North America, while hazel, hornbeam and oak prefer a warmer climate, thus populating rather the southern parts of these continents. Co-populations of all five species are frequently found in temperate climate zones 5.(Spieksma FTM. Regional European pollen calendars. D'Amato G, Spieksma FTM, Bonini S, editors. Allergenic pollen and pollinosis in Europe. Hoboken, NJ: Wiley-Blackwell; 1991. pp. 49–65) Several Betulaceae trees including alder, hazel and hornbeam have the potential to initiate sensitization to Bet v 1-like allergens in susceptible individuals resulting in the production of highly cross-reactive IgE antibodies. (Hauser, et al., 2011, Clin Exp Allergy. 41: 1804–14)

[00177] The Fagales order allergens, or Fagales allergens, as defined herein include birch pollen (Bet v 1), alder pollen (Aln g1 and Aln g4), hazel pollen (Cor a1, Cor a2, Cor a8, Cor a9, Cor a10, Cor a11, Cor a12, Cor a13, and Cor a14), hornbeam pollen (Car b1), hop-hornbeam pollen (Ost c1), chestnut pollen (Cas s1, Cas s5, Cas s8, and Cas s9), beech pollen (Fag s1) and white oak pollen (Que a1 and Que a2). Of the non-birch pollens, Aln g1, Cor a1, Car b1, Ost c1, Cas s1, Fag s1, and Que a1 are like or related to Bet v 1, i.e. Fagales related allergens. These allergens are also expressed in nuts of the Fagales trees, and in the fruits of unrelated trees belonging to the order Rosales. Cross-reactivity of these allergens may prompt symptoms of food allergy in pollen allergic patients. Exemplary cross-reactive food allergies include apple, cherry, apricot, pear, medicago, pea, soybean, tomato, celery, carrot, and asparagus. (Allergens and Allergen Immunotherapy: Subcutaneous, Sublingual, and Oral, 5th Edition. Richard F. Lockey, Dennis K. Ledford, editors. CRC Press, Taylor & Francis Group, London, NY, 2014. pp. 114, 118-119).

[00178] As used herein, the phrase "Fagales allergen" includes Fagales related allergens. In some embodiments, the "Fagales related allergen" is defined as a protein having an overall sequence homology with Bet v 1 of at least about 35%, or a sequence homology with epitope 1 of Bet v 1 of at least about 50%, or a sequence homology with epitope 2 of Bet v 1 of at least about 40%, or a sequence homology with epitope 3 of Bet v 1 of at least about 25%, or a sequence homology with epitope 4 of Bet v 1 of at least about 15%. In some embodiments, the "Fagales related allergen" is defined as a protein to which the anti-Bet v 1 antibodies cross-react, including allergens from the Rosales order.

[00179] Immunoglobulin E (IgE) is responsible for type 1 hypersensitivity, which manifests itself in allergic rhinitis, allergic conjunctivitis, hay fever, allergic asthma, bee venom allergy, and food allergies. IgE circulates in the blood and binds to high-affinity Fc receptors for IgE on basophils and mast cells. In most allergic responses, the allergens enter the body through inhalation, ingestion, or through the skin. The allergen then binds to preformed IgE already bound to the high affinity receptor on the surfaces of mast cells and basophils, resulting in cross-linking of several IgE molecules and triggering the release of histamine and other inflammatory mediators causing the various allergic symptoms.

[00180] The treatment for birch pollen allergies includes desensitization therapy, which involves repeated injections with increasing dosages of either a crude birch pollen extract, or short peptides derived from Bet v 1. Insufficiencies of allergen specific immunotherapy include long treatment duration resulting in patient compliance issues, and frequent allergic reactions (up to 30%) to the injected protein. Desensitization therapy can take several years before the treatment is considered effective. Successful treatment is dependent on composition and quality of extract, and treatment is contraindicated in patients with severe asthma/food allergies due to risk of IgE mediated severe adverse events. Accordingly, there is a need in the field of birch pollen allergy treatment for alternative strategies for treating patients sensitive to Fagales allergens, in particular Bet v 1.

[00181] Antibodies have been proposed as a general treatment strategy for allergies, since they may be able to block the entry of allergenic molecules into the mucosal tissues, or may bind the allergen before it has the opportunity to bind to the IgE bound to the high affinity receptor on mast cells or basophils, thus preventing the release of histamine and other inflammatory mediators from these cells. U.S. patent number 5,670,626 describes the use of monoclonal antibodies for the treatment of IgE-mediated allergic diseases such as allergic rhinitis, allergic asthma, and allergic conjunctivitis by blocking the binding of allergens to the mucosal tissue. U.S. patent number 6,849,259 describes the use of allergen-specific antibodies to inhibit allergic inflammation in an *in vivo* mouse model of allergy. Milk-based and egg-based antibody systems have been described. For example, US20030003133A1 discloses using milk as a carrier for allergens for inducing oral tolerance to birch pollen and other allergens. Compositions and methods for reducing an allergic response in an animal to an allergen in the environment through use of a molecule that inhibits the ability of the allergen to bind to mast cells were described in WO1994/024164A2. Other antibodies to Bet v 1 were mentioned in U.S. 2010/0034812.

[00182] The fully human antibodies described herein demonstrate specific binding to Bet v 1 and may be useful for treating patients suffering from birch pollen allergies, in particular, in patients who demonstrate sensitivity to the Bet v 1 allergen. The use of such antibodies may be an effective means of treating patients suffering from allergies to pollen from Fagales trees, or they may be used to prevent a heightened response to Bet v 1 upon secondary exposure, or the accompanying symptoms associated with the allergy, or may be used to lessen the severity and/or the duration of the allergic response associated with a primary exposure to birch pollen allergen or with the recurrence of the symptoms upon secondary exposure. They may be used alone or as adjunct therapy with other therapeutic moieties or modalities known in the art for treating such allergies, such as, but not limited to, treatment with corticosteroids or epinephrine. They may be used in conjunction with a second or third different antibody specific for Bet v 1. They may be used with allergen-specific immunotherapy (SIT). In some embodiments, the combination with SIT results is synergistically effective.

[00183] Unlike desensitization therapy, treatment with the antibodies described herein can provide effective relief within about 2 weeks of starting treatment, or within about 10 days or about 8 days of starting treatment. In combination with exposure to Bet v 1 protein or peptides, or one or more additional Fagales allergens, treatment with the fully human antibodies described herein can not only block an allergic reaction, but can more effectively or synergistically desensitize patients suffering from allergies to pollen from Fagales trees.

[00184] In certain embodiments, the antibodies of the invention are obtained from mice immunized with a primary immunogen, such as natural Bet v 1, which may be purchased commercially (*e.g.,* from Indoor Biotechnologies, VA, # NA-BV1-1), or may be produced recombinantly. The full-length amino acid sequence of Bet v 1 is shown as SEQ ID NO: 306. The full-length Bet v 1 amino acid sequence may also be found in SEQ ID NO: 314, from Uniprot: P15494.

[00185] The immunogen may be a biologically active and/or immunogenic fragment of natural, native, or recombinantly produced Bet v 1, or DNA encoding the active fragment thereof. The fragment may be derived from either the N-terminal or C-terminal of Bet v 1, or from any site within the Bet v 1 amino acid sequence.

Antigen-Binding Fragments of Antibodies

[00186] Unless specifically indicated otherwise, the term "antibody," as used herein, shall be understood to encompass antibody molecules comprising two immunoglobulin heavy

chains and two immunoglobulin light chains (*i.e.*, "full antibody molecules") as well as antigen-binding fragments thereof. The terms "antigen-binding portion" of an antibody, "antigen-binding fragment" of an antibody, and the like, as used herein, include any naturally occurring, enzymatically obtainable, synthetic, or genetically engineered polypeptide or glycoprotein that specifically binds an antigen to form a complex. The terms "antigen-binding portion" of an antibody, or "antibody fragment", as used herein, refers to one or more fragments of an antibody that retain the ability to specifically bind to Bet v 1. An antibody fragment may include a Fab fragment, a $F(ab')_2$ fragment, a Fv fragment, a dAb fragment, a fragment containing a CDR, or an isolated CDR. Antigen-binding fragments of an antibody may be derived, *e.g.*, from full antibody molecules using any suitable standard techniques such as proteolytic digestion or recombinant genetic engineering techniques involving the manipulation and expression of DNA encoding antibody variable and (optionally) constant domains. Such DNA is known and/or is readily available from, *e.g.*, commercial sources, DNA libraries (including, *e.g.*, phage-antibody libraries), or can be synthesized. The DNA may be sequenced and manipulated chemically or by using molecular biology techniques, for example, to arrange one or more variable and/or constant domains into a suitable configuration, or to introduce codons, create cysteine residues, modify, add or delete amino acids, etc.

[00187] Non-limiting examples of antigen-binding fragments include: (i) Fab fragments; (ii) F(ab')2 fragments; (iii) Fd fragments; (iv) Fv fragments; (v) single-chain Fv (scFv) molecules; (vi) dAb fragments; and (vii) minimal recognition units consisting of the amino acid residues that mimic the hypervariable region of an antibody (*e.g.*, an isolated complementarity determining region (CDR) such as a CDR3 peptide), or a constrained FR3-CDR3-FR4 peptide. Other engineered molecules, such as domain-specific antibodies, single domain antibodies, domain-deleted antibodies, chimeric antibodies, CDR-grafted antibodies, diabodies, triabodies, tetrabodies, minibodies, nanobodies (*e.g.* monovalent nanobodies, bivalent nanobodies, etc.), small modular immunopharmaceuticals (SMIPs), and shark variable IgNAR domains, are also encompassed within the expression "antigen-binding fragment," as used herein.

[00188] An antigen-binding fragment of an antibody will typically comprise at least one variable domain. The variable domain may be of any size or amino acid composition and will generally comprise at least one CDR, which is adjacent to or in frame with one or more framework sequences. In antigen-binding fragments having a V_H domain associated with a V_L domain, the V_H and V_L domains may be situated relative to one another in any suitable

arrangement. For example, the variable region may be dimeric and contain V_H - V_H, V_H - V_L or V_L - V_L dimers. Alternatively, the antigen-binding fragment of an antibody may contain a monomeric V_H or V_L domain.

[00189] In certain embodiments, an antigen-binding fragment of an antibody may contain at least one variable domain covalently linked to at least one constant domain. Non-limiting, exemplary configurations of variable and constant domains that may be found within an antigen-binding fragment of an antibody of the present invention include: (i) V_H - C_H1; (ii) V_H -C_H2; (iii) V_H -C_H3; (iv) V_H -C_H1-C_H2; (v) V_H -C_H1-C_H2-C_H3; (vi) V_H -C_H2-C_H3; (vii) V_H -C_L; (viii) V_L -C_H1; (ix) V_L -C_H2; (x) V_L -C_H3; (xi) V_L -C_H1-C_H2; (xii) V_L - C_H1-C_H2-C_H3; (xiii) V_L -C_H2-C_H3; and (xiv) V_L -C_L. In any configuration of variable and constant domains, including any of the exemplary configurations listed above, the variable and constant domains may be either directly linked to one another or may be linked by a full or partial hinge or linker region. A hinge region may consist of at least 2 (*e.g.*, 5, 10, 15, 20, 40, 60 or more) amino acids, which result in a flexible or semi-flexible linkage between adjacent variable and/or constant domains in a single polypeptide molecule. Moreover, an antigen-binding fragment of an antibody of the present invention may comprise a homo-dimer or hetero-dimer (or other multimer) of any of the variable and constant domain configurations listed above in non-covalent association with one another and/or with one or more monomeric V_H or V_L domain (*e.g.*, by disulfide bond(s)).

Preparation of Human Antibodies

[00190] Methods for generating human antibodies in transgenic mice are known in the art. Any such known methods can be used in the context of the present invention to make human antibodies that specifically bind to Bet v 1.

[00191] Using VELOCIMMUNE™ technology (see, for example, US 6,596,541, Regeneron Pharmaceuticals, VELOCIMMUNE®) or any other known method for generating monoclonal antibodies, high affinity chimeric antibodies to Bet v 1 are initially isolated having a human variable region and a mouse constant region. The VELOCIMMUNE® technology involves generation of a transgenic mouse having a genome comprising human heavy and light chain variable regions operably linked to endogenous mouse constant region loci such that the mouse produces an antibody comprising a human variable region and a mouse constant region in response to antigenic stimulation. The DNA encoding the variable regions of the heavy and light chains of the antibody are isolated and operably linked to DNA

encoding the human heavy and light chain constant regions. The DNA is then expressed in a cell capable of expressing the fully human antibody.

[00192] Generally, a VELOCIMMUNE® mouse is challenged with the antigen of interest, and lymphatic cells (such as B-cells) are recovered from the mice that express antibodies. The lymphatic cells may be fused with a myeloma cell line to prepare immortal hybridoma cell lines, and such hybridoma cell lines are screened and selected to identify hybridoma cell lines that produce antibodies specific to the antigen of interest. DNA encoding the variable regions of the heavy chain and light chain may be isolated and linked to desirable isotypic constant regions of the heavy chain and light chain. Such an antibody protein may be produced in a cell, such as a CHO cell. Alternatively, DNA encoding the antigen-specific chimeric antibodies or the variable domains of the light and heavy chains may be isolated directly from antigen-specific lymphocytes.

[00193] Initially, high affinity chimeric antibodies are isolated having a human variable region and a mouse constant region. As in the experimental section below, the antibodies are characterized and selected for desirable characteristics, including affinity, selectivity, epitope, etc. The mouse constant regions are replaced with a desired human constant region to generate the fully human antibody of the invention, for example wild-type or modified IgG1 or IgG4. While the constant region selected may vary according to specific use, high affinity antigen-binding and target specificity characteristics reside in the variable region.

[00194] In general, the antibodies of the instant invention possess very high affinities, typically possessing K_D of from about 10^{-12} through about 10^{-9} M, when measured by binding to antigen either immobilized on solid phase or in solution phase. The mouse constant regions are replaced with desired human constant regions to generate the fully human antibodies of the invention. While the constant region selected may vary according to specific use, high affinity antigen-binding and target specificity characteristics reside in the variable region.

Bioequivalents

[00195] The anti-Bet v 1 antibodies and antibody fragments of the present invention encompass proteins having amino acid sequences that vary from those of the described antibodies, but that retain the ability to bind Bet v 1. Such variant antibodies and antibody fragments comprise one or more additions, deletions, or substitutions of amino acids when compared to parent sequence, but exhibit biological activity that is essentially equivalent to that of the described antibodies. Likewise, the antibody-encoding DNA sequences of the

present invention encompass sequences that comprise one or more additions, deletions, or substitutions of nucleotides when compared to the disclosed sequence, but that encode an antibody or antibody fragment that is essentially bioequivalent to an antibody or antibody fragment of the invention.

[00196] Two antigen-binding proteins, or antibodies, are considered bioequivalent if, for example, they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose under similar experimental conditions, either single does or multiple dose. Some antibodies will be considered equivalents or pharmaceutical alternatives if they are equivalent in the extent of their absorption but not in their rate of absorption and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on, *e.g.*, chronic use, and are considered medically insignificant for the particular drug product studied.

[00197] In one embodiment, two antigen-binding proteins are bioequivalent if there are no clinically meaningful differences in their safety, purity, and potency.

[00198] In one embodiment, two antigen-binding proteins are bioequivalent if a patient can be switched one or more times between the reference product and the biological product without an expected increase in the risk of adverse effects, including a clinically significant change in immunogenicity, or diminished effectiveness, as compared to continued therapy without such switching.

[00199] In one embodiment, two antigen-binding proteins are bioequivalent if they both act by a common mechanism or mechanisms of action for the condition or conditions of use, to the extent that such mechanisms are known.

[00200] Bioequivalence may be demonstrated by *in vivo* and/or *in vitro* methods. Bioequivalence measures include, *e.g.*, (a) an *in vivo* test in humans or other mammals, in which the concentration of the antibody or its metabolites is measured in blood, plasma, serum, or other biological fluid as a function of time; (b) an *in vitro* test that has been correlated with and is reasonably predictive of human *in vivo* bioavailability data; (c) an *in vivo* test in humans or other mammals in which the appropriate acute pharmacological effect of the antibody (or its target) is measured as a function of time; and (d) in a well-controlled clinical trial that establishes safety, efficacy, or bioavailability or bioequivalence of an antibody.

[00201] Bioequivalent variants of the antibodies of the invention may be constructed by, for example, making various substitutions of residues or sequences or deleting terminal or internal residues or sequences not needed for biological activity. For example, cysteine residues not essential for biological activity can be deleted or replaced with other amino acids to prevent formation of unnecessary or incorrect intramolecular disulfide bridges upon renaturation. In other contexts, bioequivalent antibodies may include antibody variants comprising amino acid changes, which modify the glycosylation characteristics of the antibodies, *e.g.*, mutations that eliminate or remove glycosylation.

Biological Characteristics of the Antibodies

[00202] In general, the antibodies of the present invention may function by binding to Bet v 1, a fragment of Bet v 1, or to Bet v 1 and one or more Fagales allergens or Fagales related allergens.

[00203] In certain embodiments, the antibodies of the present invention may bind to an epitope or fragment located within the Bet v 1 protein, for example, an epitope or fragment encompassing amino acid residues ranging from about position 23 to about position 43 of SEQ ID NO: 306; an epitope or fragment encompassing amino acid residues ranging from about position 44 to about 56 of SEQ ID NO: 306; an epitope or fragment encompassing amino acid residues ranging from about 2 to about 19 of SEQ ID NO: 306; an epitope or fragment encompassing amino acid residues ranging from about 57 to about 70 of SEQ ID NO: 306; or an epitope or fragment encompassing amino acid residues ranging from about 81 to about 89 or about 81 to about 96 of SEQ ID NO: 306. In certain embodiments, the antibodies of the present invention may bind to at least one amino acid sequence selected from the group consisting of SEQ ID NOs: 307, 308, 309, 310, 311, and 315, wherein an epitope sequence can be extended by 1 to 5 amino acids, or about 5 to about 10 amino acids on either the C-terminal end or the N-terminal end.

[00204] In certain embodiments, the antibodies of the present invention may function by blocking or inhibiting the binding of IgE to mast cells or basophils in a patient sensitive to the Bet v 1 allergen. In certain embodiments, the antibodies provided herein inhibit or block basophil activation by, for example, at least about 70%, when compared to an isotype control antibody. In certain embodiments, the antibodies inhibit or block mast cell degranulation by, for example, at least about 70%, or at least about 75%, or at least about 80%, or at least about 85%, or at least about 90%, or at least about 95%, when compared to an isotype control antibody.

[00205] In one embodiment, described is a fully human monoclonal antibody or antigen-binding fragment thereof that binds to Bet v 1, wherein the antibody or fragment thereof exhibits one or more of the following characteristics: (i) comprises a HCVR having an amino acid sequence selected from the group consisting of SEQ ID NO: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 282, and 290, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (ii) comprises a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NO: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, and 298, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (iii) comprises a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 8, 24, 40, 56, 72, 88, 104, 120, 136, 152, 168, 184, 200, 216, 232, 248, 264, 280, 288, and 296, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 16, 32, 48, 64, 80, 96, 112, 128, 144, 160, 176, 192, 208, 224, 240, 256, 272, and 304, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (iv) comprises a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 4, 20, 36, 52, 68, 84, 100, 116, 132, 148, 164, 180, 196, 212, 228, 244, 260, 276, 284, and 292, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 6, 22, 38, 54, 70, 86, 102, 118, 134, 150, 166, 182, 198, 214, 230, 246, 262, 278, 286, and 294, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 12, 28, 44, 60, 76, 92, 108, 124, 140, 156, 172, 188, 204, 220, 236, 252, 268, and 300, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 14, 30, 46, 62, 78, 94, 110, 126, 142, 158, 174, 190, 206, 222, 238, 254, 270, and 302, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (v) binds to Bet v 1 with a K_D equal to or less than 10^{-8} or in a range from about 10^{-8} to about 10^{-11}; (vi) demonstrates efficacy in at least one animal model of anaphylaxis or inflammation; or (vii) competes with a reference antibody for binding to Bet v 1.

[00206] In one embodiment, the invention provides for the use of a combination of two or more fully human antibodies of the invention, or fragments thereof, for preparation of a composition, wherein the antibodies bind to Bet v 1, and wherein each antibody or fragment thereof contained within the composition exhibits one or more of the following characteristics: (i) comprises a HCVR having an amino acid sequence selected from the group consisting of SEQ ID NO: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 282, and 290, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (ii) comprises a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NO: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, and 298, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (iii) comprises a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 8, 24, 40, 56, 72, 88, 104, 120, 136, 152, 168, 184, 200, 216, 232, 248, 264, 280, 288, and 296, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 16, 32, 48, 64, 80, 96, 112, 128, 144, 160, 176, 192, 208, 224, 240, 256, 272, and 304, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (iv) comprises a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 4, 20, 36, 52, 68, 84, 100, 116, 132, 148, 164, 180, 196, 212, 228, 244, 260, 276, 284, and 292, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 6, 22, 38, 54, 70, 86, 102, 118, 134, 150, 166, 182, 198, 214, 230, 246, 262, 278, 286, and 294, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 12, 28, 44, 60, 76, 92, 108, 124, 140, 156, 172, 188, 204, 220, 236, 252, 268, and 300, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 14, 30, 46, 62, 78, 94, 110, 126, 142, 158, 174, 190, 206, 222, 238, 254, 270, and 302, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (v) binds to Bet v 1 with a K_D equal to or less than 10^{-8} or in a range from about 10^{-8} to about 10^{-11}; (vi) demonstrates efficacy in at least one animal

model of anaphylaxis or inflammation; or (vii) competes with a reference antibody for binding to Bet v 1.

[00207] Certain Bet v 1 antibodies of the present invention, when used alone, or in combination, are able to bind to and neutralize at least one biological effect of Bet v 1, as determined by *in vitro* or *in vivo* assays. The ability of the antibodies of the invention to bind to and neutralize the activity of Bet v 1 may be measured using any standard method known to those skilled in the art, including binding assays, or neutralization of activity (*e.g.*, protection from anaphylaxis) assays, as described herein.

[00208] Non-limiting, exemplary *in vitro* assays for measuring binding activity are illustrated in Example 3, herein. In Example 3, the binding affinities and kinetic constants of human anti-Bet v 1 antibodies were determined by surface plasmon resonance.

[00209] The Bet v 1 proteins or peptides may be modified to include addition or substitution of certain residues for tagging or for purposes of conjugation to carrier molecules, such as, KLH. For example, a cysteine may be added at either the N terminal or C terminal end of a peptide, or a linker sequence may be added to prepare the peptide for conjugation to, for example, KLH for immunization. The antibodies specific for Bet v 1 may contain no additional labels or moieties, or they may contain an N-terminal or C-terminal label or moiety. In one embodiment, the label or moiety is biotin. In a binding assay, the location of a label (if any) may determine the orientation of the peptide relative to the surface upon which the peptide is bound. For example, if a surface is coated with avidin, a peptide containing an N-terminal biotin will be oriented such that the C-terminal portion of the peptide will be distal to the surface.

Epitope Mapping and Related Technologies

[00210] The term "epitope," as used herein, refers to an antigenic determinant that interacts with a specific antigen binding site in the variable region of an antibody molecule known as a paratope. A single antigen may have more than one epitope. Thus, different antibodies may bind to different areas on an antigen and may have different biological effects. Epitopes may be either conformational or linear. A conformational epitope is produced by spatially juxtaposed amino acids from different segments of the linear polypeptide chain. A linear epitope is one produced by adjacent amino acid residues in a polypeptide chain. In certain circumstance, an epitope may include moieties of saccharides, phosphoryl groups, or sulfonyl groups on the antigen.

[00211] Provided herein are anti-Bet v 1 antibodies which interact with one or more amino acids found within the Bet v 1 molecule including, e.g., any fragment of Bet v 1 shown in SEQ ID NO: 306, or within comparable regions of a recombinantly produced Bet v 1 protein. The epitope to which the antibodies bind may consist of a single contiguous sequence of 3 or more (e.g., 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more) amino acids located within the Bet v 1 molecule. Exemplary contiguous sequences include amino acid residues ranging from about position 23 to about position 44 of SEQ ID NO: 306; amino acid residues ranging from about position 23 to about position 43 of SEQ ID NO: 306; amino acid residues ranging from about position 23 to about position 38 of SEQ ID NO: 306; amino acid residues ranging from about position 23 to about position 41 of SEQ ID NO: 306; amino acid residues ranging from about position 26 to about position 43 of SEQ ID NO: 306; amino acid residues ranging from about position 29 to about position 43 of SEQ ID NO: 306; amino acid residues ranging from about position 44 to about position 70 of SEQ ID NO: 306; amino acid residues ranging from about position 44 to about position 56 of SEQ ID NO: 306; amino acid residues ranging from about position 45 to about position 56 of SEQ ID NO: 306; amino acid residues ranging from about position 2 to about position 19 of SEQ ID NO: 306; amino acid residues ranging from about position 5 to about position 10 of SEQ ID NO: 306; amino acid residues ranging from about position 5 to about position 19 of SEQ ID NO: 306; amino acid residues ranging from about position 8 to about position 19 of SEQ ID NO: 306; amino acid residues ranging from about position 11 to about position 19 of SEQ ID NO: 306; amino acid residues ranging from about position 57 to about position 70 of SEQ ID NO: 306; amino acid residues ranging from about position 57 to about position 66 of SEQ ID NO: 306; amino acid residues ranging from about position 81 to about position 96 of SEQ ID NO: 306; amino acid residues ranging from about position 84 to about position 96 of SEQ ID NO: 306; amino acid residues ranging from about position 85 to about position 96 of SEQ ID NO: 306; and amino acid residues ranging from about position 81 to about position 89 of SEQ ID NO: 306. Further exemplary contiguous sequences include at least one amino acid sequence selected from the group consisting of SEQ ID NOs: 307, 308, 309, 310, 311, and 315, wherein such sequence can be extended by about 1 to about 5 amino acids, or about 5 to about 10 amino acids, on either the C-terminal end or the N-terminal end. Alternatively, the epitope may consist of a plurality of non-contiguous amino acids (or amino acid sequences) located within the Bet v 1 molecule (e.g. a conformational epitope).

[00212] Various techniques known to persons of ordinary skill in the art can be used to determine whether an antibody "interacts with one or more amino acids" within a polypeptide

or protein. Exemplary techniques include, for example, routine cross-blocking assays, such as that described in Antibodies, Harlow and Lane (Cold Spring Harbor Press, Cold Spring Harb., NY). Other methods include alanine scanning mutational analysis, peptide blot analysis (Reineke (2004) Methods Mol Biol 248:443-63), peptide cleavage analysis crystallographic studies and NMR analysis. In addition, methods such as epitope excision, epitope extraction and chemical modification of antigens can be employed (Tomer (2000) Protein Science 9: 487-496). Another method that can be used to identify the amino acids within a polypeptide with which an antibody interacts is hydrogen/deuterium exchange detected by mass spectrometry. In general terms, the hydrogen/deuterium exchange method involves deuterium-labeling the protein of interest, followed by binding the antibody to the deuterium-labeled protein. Next, the protein/antibody complex is transferred to water and exchangeable protons within amino acids that are protected by the antibody complex undergo deuterium-to-hydrogen back-exchange at a slower rate than exchangeable protons within amino acids that are not part of the interface. As a result, amino acids that form part of the protein/antibody interface may retain deuterium and therefore exhibit relatively higher mass compared to amino acids not included in the interface. After dissociation of the antibody, the target protein is subjected to protease cleavage and mass spectrometry analysis, thereby revealing the deuterium-labeled residues which correspond to the specific amino acids with which the antibody interacts. *See, e.g.*, Ehring (1999) *Analytical Biochemistry* 267(2):252-259; Engen and Smith (2001) *Anal. Chem. 73*:256A-265A. X-ray crystallography of the antigen/antibody complex may also be used for epitope mapping purposes.

[00213] Modification-Assisted Profiling (MAP), also known as Antigen Structure-based Antibody Profiling (ASAP) is a method that categorizes large numbers of monoclonal antibodies (monoclonal antibodies) directed against the same antigen according to the similarities of the binding profile of each antibody to chemically or enzymatically modified antigen surfaces (US 2004/0101920). Each category may reflect a unique epitope either distinctly different from or partially overlapping with epitope represented by another category. This technology allows rapid filtering of genetically identical antibodies, such that characterization can be focused on genetically distinct antibodies. When applied to hybridoma screening, MAP may facilitate identification of rare hybridoma clones that produce monoclonal antibodies having the desired characteristics. MAP may be used to sort the antibodies described into groups of antibodies binding different epitopes.

[00214] In certain embodiments, the anti-Bet v 1 antibodies or antigen-binding fragments thereof bind an epitope within Bet v 1, in natural or native form, as exemplified in

SEQ ID NO: 306 or SEQ ID NO: 314 (Bet v 1 amino acid sequence from Uniprot: P15494), or recombinantly produced, or to a fragment thereof. In certain embodiments, the antibodiesdescribed, as shown in Table 1, interact with at least one amino acid sequence selected from the group consisting of amino acid residues ranging from about position 23 to about position 44 of SEQ ID NO: 306; amino acid residues ranging from about position 23 to about position 43 of SEQ ID NO: 306; amino acid residues ranging from about position 23 to about position 38 of SEQ ID NO: 306; amino acid residues ranging from about position 23 to about position 41 of SEQ ID NO: 306; amino acid residues ranging from about position 26 to about position 43 of SEQ ID NO: 306; amino acid residues ranging from about position 29 to about position 43 of SEQ ID NO: 306; amino acid residues ranging from about position 44 to about position 70 of SEQ ID NO: 306; amino acid residues ranging from about position 44 to about position 56 of SEQ ID NO: 306; amino acid residues ranging from about position 45 to about position 56 of SEQ ID NO: 306; amino acid residues ranging from about position 2 to about position 19 of SEQ ID NO: 306; amino acid residues ranging from about position 5 to about position 10 of SEQ ID NO: 306; amino acid residues ranging from about position 5 to about position 19 of SEQ ID NO: 306; amino acid residues ranging from about position 8 to about position 19 of SEQ ID NO: 306; amino acid residues ranging from about position 11 to about position 19 of SEQ ID NO: 306; amino acid residues ranging from about position 57 to about position 70 of SEQ ID NO: 306; amino acid residues ranging from about position 57 to about position 66 of SEQ ID NO: 306; amino acid residues ranging from about position 81 to about position 96 of SEQ ID NO: 306; amino acid residues ranging from about position 84 to about position 96 of SEQ ID NO: 306; amino acid residues ranging from about position 85 to about position 96 of SEQ ID NO: 306; and amino acid residues ranging from about position 81 to about position 89 of SEQ ID NO: 306. These regions are further exemplified in SEQ ID NOs: 307, 308, 309, 310, 311 and 315.

[00215] Also described are anti-Bet v 1 antibodies that bind to the same epitope, or a portion of the epitope, as any of the specific exemplary antibodies described herein in Table 1, or an antibody having the CDR sequences of any of the exemplary antibodies described in Table 1. Likewise, described are anti-Bet v 1 antibodies that compete for binding to Bet v 1 or a Bet v 1 fragment with any of the specific exemplary antibodies described herein in Table 1, or an antibody having the CDR sequences of any of the exemplary antibodies described in Table 1.

[00216] One can easily determine whether an antibody binds to the same epitope as, or competes for binding with, a reference anti-Bet v 1 antibody by using routine methods known

in the art. For example, to determine if a test antibody binds to the same epitope as a reference anti-Bet v 1 antibody of the invention, the reference antibody is allowed to bind to a Bet v 1 protein or peptide under saturating conditions. Next, the ability of a test antibody to bind to the Bet v 1 molecule is assessed. If the test antibody is able to bind to Bet v 1 following saturation binding with the reference anti-Bet v 1 antibody, it can be concluded that the test antibody binds to a different epitope than the reference anti-Bet v 1 antibody. On the other hand, if the test antibody is not able to bind to the Bet v 1 molecule following saturation binding with the reference anti-Bet v 1 antibody, then the test antibody may bind to the same epitope as the epitope bound by the reference anti-Bet v 1 antibody of the invention.

[00217] To determine if an antibody competes for binding with a reference anti-Bet v 1 antibody, the above-described binding methodology is performed in two orientations: In a first orientation, the reference antibody is allowed to bind to a Bet v 1 molecule under saturating conditions followed by assessment of binding of the test antibody to the Bet v 1 molecule. In a second orientation, the test antibody is allowed to bind to a Bet v 1 molecule under saturating conditions followed by assessment of binding of the reference antibody to the Bet v 1 molecule. If, in both orientations, only the first (saturating) antibody is capable of binding to the Bet v 1 molecule, then it is concluded that the test antibody and the reference antibody compete for binding to Bet v 1. As will be appreciated by a person of ordinary skill in the art, an antibody that competes for binding with a reference antibody may not necessarily bind to the identical epitope as the reference antibody, but may sterically block binding of the reference antibody by binding an overlapping or adjacent epitope.

[00218] Two antibodies bind to the same or overlapping epitope if each competitively inhibits (blocks) binding of the other to the antigen. That is, a 1-, 5-, 10-, 20- or 100-fold excess of one antibody inhibits binding of the other by at least 50% but preferably 75%, 90% or even 99% as measured in a competitive binding assay (see, *e.g.,* Junghans *et al.*, Cancer Res. 1990 50:1495-1502). Alternatively, two antibodies have the same epitope if essentially all amino acid mutations in the antigen that reduce or eliminate binding of one antibody reduce or eliminate binding of the other. Two antibodies have overlapping epitopes if some amino acid mutations that reduce or eliminate binding of one antibody reduce or eliminate binding of the other.

[00219] Additional routine experimentation (*e.g.*, peptide mutation and binding analyses) can then be carried out to confirm whether the observed lack of binding of the test antibody is in fact due to binding to the same epitope as the reference antibody or if steric blocking (or another phenomenon) is responsible for the lack of observed binding.

Experiments of this sort can be performed using ELISA, RIA, surface plasmon resonance, flow cytometry or any other quantitative or qualitative antibody-binding assay available in the art.

Immunoconjugates

[00220] The invention encompasses a human anti-Bet v 1 monoclonal antibody conjugated to a therapeutic moiety ("immunoconjugate"), such as an agent that is capable of reducing the severity of an allergic response to the Bet v 1 allergen, or in an environment where Fagales trees are present, or to ameliorate at least one symptom associated with exposure to birch pollen or to the Bet v 1 allergen, including rhinitis, conjunctivitis, or breathing difficulties, or the severity thereof. Such an agent may be a corticosteroid, a second different antibody to Bet v 1, or a vaccine. The type of therapeutic moiety that may be conjugated to the Bet v 1 antibody will take into account the condition to be treated and the desired therapeutic effect to be achieved. Alternatively, if the desired therapeutic effect is to treat the sequelae or symptoms associated with exposure to the Bet v 1 allergen, or any other condition resulting from such exposure, such as, but not limited to, rhinitis or conjunctivitis, it may be advantageous to conjugate an agent appropriate to treat the sequelae or symptoms of the condition, or to alleviate any side effects of the antibodies of the invention. Examples of suitable agents for forming immunoconjugates are known in the art, see for example, WO 05/103081.

Therapeutic Administration and Formulations

[00221] The invention provides therapeutic compositions comprising the anti-Bet v 1 antibodies or antigen-binding fragments thereof of the present invention. The administration of therapeutic compositions in accordance with the invention will be administered via a suitable route including, but not limited to, intravenously, subcutaneously, intramuscularly, intranasally, with suitable carriers, excipients, and other agents that are incorporated into formulations to provide improved transfer, delivery, tolerance, and the like. A multitude of appropriate formulations can be found in the formulary known to all pharmaceutical chemists: Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA. These formulations include, for example, powders, pastes, ointments, jellies, waxes, oils, lipids, lipid (cationic or anionic) containing vesicles (such as LIPOFECTIN™), DNA conjugates, anhydrous absorption pastes, oil-in-water and water-in-oil emulsions, emulsions carbowax (polyethylene glycols of various molecular weights), semi-solid gels, and semi-

solid mixtures containing carbowax. See also Powell *et al.* "Compendium of excipients for parenteral formulations" PDA (1998) J Pharm Sci Technol 52:238-311.

[00222] The dose of antibody may vary depending upon the age and the size of a patient to be administered, target disease, conditions, route of administration, and the like. When the antibody of the present invention is used for treating the rhinitis or conjunctivitis associated with exposure to pollen from a Fagales tree, or birch pollen, or Bet v 1, in an individual having a sensitivity to Bet v 1, or for preventing an anaphylactic response to the Fagales allergen, or for lessening the severity of the allergic response, it is advantageous to intravenously administer the antibody of the present invention normally at a single dose of about 0.01 to about 30 mg/kg body weight, more preferably about 0.02 to about 7, about 0.03 to about 5, or about 0.05 to about 3 mg/kg body weight. Depending on the severity of the condition, the frequency and the duration of the treatment can be adjusted. In certain embodiments, the antibody or antigen-binding fragment thereof of the invention can be administered as an initial dose of at least about 0.1 mg to about 800 mg, about 1 to about 500 mg, about 5 to about 300 mg, or about 10 to about 200 mg, to about 100 mg, or to about 50 mg. In certain embodiments, the initial dose may be followed by administration of a second or a plurality of subsequent doses of the antibody or antigen-binding fragment thereof in an amount that can be approximately the same or less than that of the initial dose, wherein the subsequent doses are separated by at least 1 day to 3 days; at least one week, at least 2 weeks; at least 3 weeks; at least 4 weeks; at least 5 weeks; at least 6 weeks; at least 7 weeks; at least 8 weeks; at least 9 weeks; at least 10 weeks; at least 12 weeks; or at least 14 weeks.

[00223] Various delivery systems are known and can be used to administer the pharmaceutical composition of the invention, *e.g.,* encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the mutant viruses, receptor mediated endocytosis (see, *e.g.*, Wu *et al.,* 1987, J. Biol. Chem. 262:4429-4432). Methods of introduction include, but are not limited to, intradermal, transdermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural and oral routes. The composition may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (*e.g.,* oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local.

[00224] The pharmaceutical composition can be also delivered in a vesicle, in particular a liposome (see, for example, Langer, 1990, Science 249: 1527-1533).

[00225] In certain situations, the pharmaceutical composition can be delivered in a controlled release system. In one embodiment, a pump may be used. In another embodiment, polymeric materials can be used. In yet another embodiment, a controlled release system can be placed in proximity of the composition's target, thus requiring only a fraction of the systemic dose.

[00226] The injectable preparations may include dosage forms for intravenous, subcutaneous, intracutaneous and intramuscular injections, drip infusions, etc. These injectable preparations may be prepared by methods publicly known. For example, the injectable preparations may be prepared, *e.g.*, by dissolving, suspending or emulsifying the antibody or its salt described above in a sterile aqueous medium or an oily medium conventionally used for injections. As the aqueous medium for injections, there are, for example, physiological saline, an isotonic solution containing glucose and other auxiliary agents, etc., which may be used in combination with an appropriate solubilizing agent such as an alcohol (*e.g.*, ethanol), a polyalcohol (e.g., propylene glycol, polyethylene glycol), a nonionic surfactant [e.g., polysorbate 80, HCO-50 (polyoxyethylene (50 mol) adduct of hydrogenated castor oil)], etc. As the oily medium, there are employed, *e.g.*, sesame oil, soybean oil, etc., which may be used in combination with a solubilizing agent such as benzyl benzoate, benzyl alcohol, etc. The injection thus prepared is preferably filled in an appropriate ampoule.

[00227] A pharmaceutical composition of the present invention can be delivered subcutaneously or intravenously with a standard needle and syringe. In addition, with respect to subcutaneous delivery, a pen delivery device readily has applications in delivering a pharmaceutical composition of the present invention. Such a pen delivery device can be reusable or disposable. A reusable pen delivery device generally utilizes a replaceable cartridge that contains a pharmaceutical composition. Once all of the pharmaceutical composition within the cartridge has been administered and the cartridge is empty, the empty cartridge can readily be discarded and replaced with a new cartridge that contains the pharmaceutical composition. The pen delivery device can then be reused. In a disposable pen delivery device, there is no replaceable cartridge. Rather, the disposable pen delivery device comes prefilled with the pharmaceutical composition held in a reservoir within the device. Once the reservoir is emptied of the pharmaceutical composition, the entire device is discarded.

[00228] Numerous reusable pen and autoinjector delivery devices have applications in the subcutaneous delivery of a pharmaceutical composition of the present invention.

Examples include, but certainly are not limited to AUTOPEN™ (Owen Mumford, Inc., Woodstock, UK), DISETRONIC™ pen (Disetronic Medical Systems, Burghdorf, Switzerland), HUMALOG MIX 75/25™ pen, HUMALOG™ pen, HUMALIN 70/30™ pen (Eli Lilly and Co., Indianapolis, IN), NOVOPEN™ I, II and III (Novo Nordisk, Copenhagen, Denmark), NOVOPEN JUNIOR™ (Novo Nordisk, Copenhagen, Denmark), BD™ pen (Becton Dickinson, Franklin Lakes, NJ), OPTIPEN™, OPTIPEN PRO™, OPTIPEN STARLET™, and OPTICLIK™ (sanofi-aventis, Frankfurt, Germany), to name only a few. Examples of disposable pen delivery devices having applications in subcutaneous delivery of a pharmaceutical composition of the present invention include, but certainly are not limited to the SOLOSTAR™ pen (sanofi-aventis), the FLEXPEN™ (Novo Nordisk), and the KWIKPEN™ (Eli Lilly), the SURECLICK ™ Autoinjector (Amgen, Thousand Oaks, CA), the PENLET ™ (Haselmeier, Stuttgart, Germany), the EPIPEN (Dey, L.P.) and the HUMIRA ™ Pen (Abbott Labs, Abbott Park, IL), to name only a few.

[00229] Advantageously, the pharmaceutical compositions for oral or parenteral use described above are prepared into dosage forms in a unit dose suited to fit a dose of the active ingredients. Such dosage forms in a unit dose include, for example, tablets, pills, capsules, injections (ampoules), suppositories, etc. The amount of the aforesaid antibody contained is generally about 5 to about 500 mg per dosage form in a unit dose; especially in the form of injection, it is preferred that the aforesaid antibody is contained in about 5 to about 100 mg and in about 10 to about 250 mg for the other dosage forms.

Therapeutic Uses of the Antibodies

[00230] Due to their interaction with Bet v 1, the present antibodies are useful for treating the primary response following exposure of an individual to Fagales allergen, birch pollen, or to an environment containing the Bet v 1 protein, or at least one symptom associated with the allergic response, such as itchy eyes, conjunctivitis, rhinitis, wheezing, breathing difficulties, or for preventing a secondary response to the Bet v 1 allergen, including a more serious anaphylactic response, or for lessening the severity, duration, and/or frequency of symptoms following reexposure to the Fagales allergen. Accordingly, it is envisioned that the antibodies of the present invention may be used prophylactically or therapeutically.

[00231] In yet a further embodiment of the invention the present antibodies are used for the preparation of a pharmaceutical composition for treating patients suffering from a sensitivity to birch pollen or an extract thereof and/or the Bet v 1 protein. In yet another

embodiment of the invention the present antibodies are used for the preparation of a pharmaceutical composition for reducing the severity of primary exposure to Bet v 1, or for reducing the severity, duration of, and/or number of allergic responses to Bet v 1. In a further embodiment of the invention the present antibodies are used as adjunct therapy with any other agent useful for treating Fagales allergens, including corticosteroids, vaccines, allergen specific immunotherapy (SIT), or any other palliative therapy known to those skilled in the art.

Combination Therapies

[00232] Combination therapies may include an anti-Bet v 1 antibody of the invention and any additional therapeutic agent that may be advantageously combined with an antibody of the invention, or with a biologically active fragment of an antibody of the invention.

[00233] For example, a second therapeutic agent may be employed to aid in reducing the allergic symptoms following exposure to a Fagales allergen, birch pollen or an extract thereof, or Bet v 1, or exposure to an environment in which Fagales trees are present and blooming, such as a corticosteroid. The antibodies may also be used in conjunction with other therapies, such as a vaccine specific for the Bet v 1 allergen. The additional therapeutically active component(s) may be administered prior to, concurrent with, or after the administration of the anti-Bet v 1 antibody of the present invention. For purposes of the present disclosure, such administration regimens are considered the administration of an anti-Bet v 1 antibody "in combination with" a second therapeutically active component.

Allergen-specific Immunotherapy (SIT)

[00234] As used herein, the expressions "allergen-specific immunotherapy", "specific immunotherapy", "SIT", "SIT regimen", and the like, refer to the repeated administration of an allergen to a patient over time as means for treating or preventing allergies and allergic reactions, or to reduce or eliminate allergic responses. In a typical SIT regimen, small amounts of allergen are initially administered to an allergic patient, followed by administration of increased amounts of allergen. In certain instances, the SIT regimen comprises at least two consecutive phases: (1) an up-dosing phase, and (2) a maintenance phase. In the up-dosing phase, increasing doses of allergen are administered until an effective and safe dose is achieved. The dose that is established at the end of the up-dosing phase is then administered to the patient throughout the course of the maintenance phase. The duration of the up-dosing phase can be several weeks or several months. In certain embodiments,

however, the up-dosing phase is of substantially shorter duration (*e.g.*, less than one week, less than 6 days, less than 5 days, less than 4 days, less than 3 days, or less than 2 days). SIT regimens comprising an up-dosing phase of less than 5 days are sometimes referred to as "Rush" immunotherapy or "Rush SIT". The maintenance phase of an SIT regimen can last several weeks, several months, several years, or indefinitely.

Administration Regimens

[00235] According to certain embodiments of the present invention, multiple doses of one or more anti-Bet v 1 antibodies (an antibody combination) may be administered to a patient over a defined time course. The methods according to this aspect of the invention comprise sequentially administering to a patient multiple doses of an antibody, antibody combination. As used herein, "sequentially administering" means that each dose of an antibody or antibody combination is administered to the patient at a different point in time, *e.g.*, on different days separated by a predetermined interval (*e.g.*, hours, days, weeks or months). The present invention includes methods, which comprise sequentially administering to the patient a single initial dose of an antibody or antibody combination followed by one or more secondary doses of the antibody, and optionally followed by one or more tertiary doses of the antibody.

[00236] The terms "initial dose," "secondary doses," and "tertiary doses," refer to the temporal sequence of administration of an antibody or antibody combination provided herein. Thus, the "initial dose" is the dose which is administered at the beginning of the treatment regimen (also referred to as the "baseline dose"); the "secondary doses" are the doses which are administered after the initial dose; and the "tertiary doses" are the doses which are administered after the secondary doses. The initial, secondary, and tertiary doses may all contain the same amount of an antibody or antibody combination but generally may differ from one another in terms of frequency of administration. In certain embodiments, however, the amount of an antibody or antibody combination, contained in the initial, secondary and/or tertiary doses varies from one another (*e.g.*, adjusted up or down as appropriate) during the course of treatment. In certain embodiments, two or more (*e.g.*, 2, 3, 4, or 5) doses are administered at the beginning of the treatment regimen as "loading doses" followed by subsequent doses that are administered on a less frequent basis (*e.g.*, "maintenance doses").

[00237] In one exemplary embodiment of the present invention, each secondary and/or tertiary dose is administered 1 to 26 (*e.g.*, 1, 1½, 2, 2½, 3, 3½, 4, 4½, 5, 5½, 6, 6½, 7, 7½, 8, 8½, 9, 9½, 10, 10½, 11, 11½, 12, 12½, 13, 13½, 14, 14½, 15, 15½, 16, 16½, 17, 17½, 18,

18½, 19, 19½, 20, 20½, 21, 21½, 22, 22½, 23, 23½, 24, 24½, 25, 25½, 26, 26½, or more) weeks after the immediately preceding dose. The phrase "the immediately preceding dose," as used herein, means, in a sequence of multiple administrations, the dose of an antibody or antibody combination, which is administered to a patient prior to the administration of the very next dose in the sequence with no intervening doses.

[00238] The methods according to this aspect of the invention may comprise administering to a patient any number of secondary and/or tertiary doses of an antibody or antibody combination. For example, in certain embodiments, only a single secondary dose is administered to the patient. In other embodiments, two or more (*e.g.*, 2, 3, 4, 5, 6, 7, 8, or more) secondary doses are administered to the patient. Likewise, in certain embodiments, only a single tertiary dose is administered to the patient. In other embodiments, two or more (*e.g.*, 2, 3, 4, 5, 6, 7, 8, or more) tertiary doses are administered to the patient.

[00239] In embodiments involving multiple secondary doses, each secondary dose may be administered at the same frequency as the other secondary doses. For example, each secondary dose may be administered to the patient 1 to 2 weeks after the immediately preceding dose. Similarly, in embodiments involving multiple tertiary doses, each tertiary dose may be administered at the same frequency as the other tertiary doses. For example, each tertiary dose may be administered to the patient 2 to 4 weeks after the immediately preceding dose. Alternatively, the frequency at which the secondary and/or tertiary doses are administered to a patient can vary over the course of the treatment regimen. The frequency of administration may also be adjusted during the course of treatment by a physician depending on the needs of the individual patient following clinical examination.

Diagnostic Uses of the Antibodies

[00240] The anti-Bet v 1 antibodies of the present invention may also be used to detect and/or measure Bet v 1 in a sample, *e.g.*, for diagnostic purposes. It is envisioned that confirmation of an allergic response thought to be caused by Bet v 1 may be made by measuring the presence of either Bet v 1 through use of any one or more of the antibodies of the invention. Exemplary diagnostic assays for Bet v 1 may comprise, *e.g.*, contacting a sample, obtained from a patient, with an anti-Bet v 1 antibody of the invention, wherein the anti-Bet v 1 antibody is labeled with a detectable label or reporter molecule or used as a capture ligand to selectively isolate Bet v 1 protein from patient samples. Alternatively, an unlabeled anti-Bet v 1 antibody can be used in diagnostic applications in combination with a secondary antibody which is itself detectably labeled. The detectable label or reporter

molecule can be a radioisotope, such as ^{3}H, ^{14}C, ^{32}P, ^{35}S, or ^{125}I; a fluorescent or chemiluminescent moiety such as fluorescein isothiocyanate, or rhodamine; or an enzyme such as alkaline phosphatase, β-galactosidase, horseradish peroxidase, or luciferase. Specific exemplary assays that can be used to detect or measure Bet v 1 in a sample include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence-activated cell sorting (FACS).

[00241] Samples that can be used in Bet v 1 diagnostic assays according to the present invention include any tissue or fluid sample obtainable from a patient, which contains detectable quantities of Bet v 1 protein, or fragments thereof, under normal or pathological conditions. Generally, levels of Bet v 1 in a particular sample obtained from a healthy/non-allergic patient (*e.g.*, a patient not afflicted with a sensitivity associated with the presence of Bet v 1) will be measured to initially establish a baseline, or standard, level of Bet v 1. This baseline level of Bet v 1 can then be compared against the levels of Bet v 1 measured in samples obtained from individuals suspected of having a sensitivity to Bet v 1 in birch pollen, or symptoms associated with such condition.

[00242] While the invention has been particularly shown and described with reference to a number of embodiments, it would be understood by those skilled in the art that changes in the form and details may be made to the various embodiments disclosed herein without departing from the spirit and scope of the invention and that the various embodiments disclosed herein are not intended to act as limitations on the scope of the claims.

EXAMPLES

[00243] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the methods and compositions of the invention, and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

Example 1: Generation of Human Antibodies to Bet v 1

[00244] An immunogen comprising any one of the following can be used to generate antibodies to Bet v 1. In certain embodiments, the antibodies of the invention are obtained

from mice immunized with a primary immunogen, such as full length natural Bet v 1 (nBet v 1), which may be purchased commercially (*e.g.,* from Stallergenes Greer, Lenoir, NC, # XP527D3A25), or isolated from birch pollen (See, for example, Buters, et al. (2012), Atomospheric Environment 55:496-505), or which may be produced recombinantly (See GenBank accession number P 15494 for the full length amino acid sequence of Bet v 1), or fragments of the Bet v 1 protein, followed by immunization with a secondary immunogen, or with an immunogenically active fragment of the natural protein. Various constructs may be prepared using portions of the Bet v 1 protein known to those skilled in the art. These constructs may be used alone, or in various combinations to elicit antibody responses *in vivo*. For example, recombinant Bet v 1 constructs, such as those exemplified in SEQ ID NOs: 307, 308, 309, 310, 311, and 315, or fragments thereof, may be used as immunogens.

[00245] In certain embodiments, the antibodies of the invention are obtained from mice immunized with a primary immunogen, such as a biologically active and/or immunogenic fragment of natural Bet v 1, or DNA encoding the active fragment thereof. The fragment may be derived from the N-terminal or C-terminal portion of Bet v 1.

[00246] In certain embodiments, the recombinant Bet v 1 protein constructs used in the studies described herein may also include a C-terminal tag (myc-myc-hexahistidine tag) as indicated below. In other embodiments, the recombinant Bet v 1 protein construct includes amino acids G2 through N160 of Uniprot P15494. In some embodiments, the construct comprises an S85A substitution. The proteins were expressed in Chinese hamster ovary (CHO) cells. An exogenous signal sequence used to promote expression in CHO cells is not included in the sequence listings.

[00247] In certain embodiments, the immunogen may be a Bet v 1 fragment or fusion protein that comprises any one or more of the following: i) amino acid residues 23-43 of Bet v 1 (see Uniprot P15494 and also SEQ ID NO: 307); ii) amino acid residues 44-56 of Bet v 1 (see Uniprot P15494 and also SEQ ID NO: 308); iii) amino acid residues 2-19 of Bet v 1 (see Uniprot P15494 and also SEQ ID NO: 309); iv) amino acid residues 57-70 of Bet v 1 (see Uniprot P15494 and also SEQ ID NO: 310); v) amino acid residues 81-89 of Bet v 1 ((see Uniprot P15494 and also SEQ ID NO: 311) and vi) amino acid residues 81-96 of Bet v 1 ((see Uniprot P15494 and also SEQ ID NO: 315).

[00248] In certain embodiments, antibodies that bind specifically to Bet v 1 may be prepared using fragments of the above-noted regions, or peptides that extend beyond the designated regions by about 5 to about 20 amino acid residues from either, or both, the N or C terminal ends of the regions described herein. In certain embodiments, any combination of

the above-noted regions or fragments thereof may be used in the preparation of Bet v 1 specific antibodies. In certain embodiments, any one or more of the above-noted regions of Bet v 1, or fragments thereof may be used for preparing monospecific, bispecific, or multispecific antibodies.

[00249] The full-length proteins, or fragments thereof, that were used as immunogens, as noted above, were administered directly, with an adjuvant to stimulate the immune response, to a VELOCIMMUNE® mouse comprising DNA encoding human immunoglobulin heavy and kappa light chain variable regions.

[00250] Anti-Bet v 1 antibodies were isolated directly from antigen-positive B cells without fusion to myeloma cells, as described in U.S. Patent 7,582,298. Using this method, several fully human anti-Bet v 1 antibodies (*i.e.*, antibodies possessing human variable domains and human constant domains) were obtained; exemplary antibodies generated in this manner were designated as follows: H4H16943P, H4H16946P, H4H16950P, H4H16960P, H4H16967P, H4H16971P, H4H16979P, H4H16987P, H4H16991P, H4H16992P, H4H17001P, H4H17015P, H4H17027P, H4H17028P, H4H17031P, H4H17033P, H4H17038P2, H4H17045P2, H4H17067P2, and H4H17082P2.

[00251] The biological properties of the exemplary antibodies generated in accordance with the methods of this Example are described in detail in the Examples set forth below.

Example 2: Heavy and Light Chain Amino Acid Sequences

[00252] Table 1a provides the amino acid sequence identifiers of the heavy and light chain variable regions and CDRs of selected anti-Bet v 1 antibodies. Table 1b provides the nucleic acid sequence identifiers of the heavy and light chain variable regions and CDRs of selected anti-Bet v 1 antibodies.

Table 1a: Amino Acid Sequence Identifiers

	SEQ ID NOs:							
Antibody Designation	**HCVR**	**HCDR1**	**HCDR2**	**HCDR3**	**LCVR**	**LCDR1**	**LCDR2**	**LCDR3**
H4H16943P	2	4	6	8	10	12	14	16
H4H16946P	18	20	22	24	26	28	30	32
H4H16950P	34	36	38	40	42	44	46	48
H4H16960P	50	52	54	56	58	60	62	64
H4H16967P	66	68	70	72	74	76	78	80
H4H16971P	82	84	86	88	90	92	94	96
H4H17038P2	98	100	102	104	106	108	110	112
H4H16987P	114	116	118	120	122	124	126	128

H4H16991P	130	132	134	136	138	140	142	144
H4H16992P	146	148	150	152	154	156	158	160
H4H17001P	162	164	166	168	170	172	174	176
H4H17015P	178	180	182	184	186	188	190	192
H4H17027P	194	196	198	200	202	204	206	208
H4H17028P	210	212	214	216	218	220	222	224
H4H17031P	226	228	230	232	234	236	238	240
H4H17033P	242	244	246	248	250	252	254	256
H4H16979P	258	260	262	264	266	268	270	272
H4H17045P2	274	276	278	280	266	268	270	272
H4H17067P2	282	284	286	288	266	268	270	272
H4H17082P2	290	292	294	296	298	300	302	304

Table 1b: Nucleic Acid Sequence Identifiers

	SEQ ID NOs:							
Antibody Designation	**HCVR**	**HCDR1**	**HCDR2**	**HCDR3**	**LCVR**	**LCDR1**	**LCDR2**	**LCDR3**
H4H16943P	1	3	5	7	9	11	13	15
H4H16946P	17	19	21	23	25	27	29	31
H4H16950P	33	35	37	39	41	43	45	47
H4H16960P	49	51	53	55	57	59	61	63
H4H16967P	65	67	69	71	73	75	77	79
H4H16971P	81	83	85	87	89	91	93	95
H4H17038P2	97	99	101	103	105	107	109	111
H4H16987P	113	115	117	119	121	123	125	127
H4H16991P	129	131	133	135	137	139	141	143
H4H16992P	145	147	149	151	153	155	157	159
H4H17001P	161	163	165	167	169	171	173	175
H4H17015P	177	179	181	183	185	187	189	191
H4H17027P	193	195	197	199	201	203	205	207
H4H17028P	209	211	213	215	217	219	221	223
H4H17031P	225	227	229	231	233	235	237	239
H4H17033P	241	243	245	247	249	251	253	255
H4H16979P	257	259	261	263	265	267	269	271
H4H17045P2	273	275	277	279	265	267	269	271
H4H17067P2	281	283	285	287	265	267	269	271
H4H17082P2	289	291	293	295	297	299	301	303

[00253] Antibodies are typically referred to herein according to the following nomenclature: Fc prefix (*e.g.* "H4H," "H2M," etc.), followed by a numerical identifier (*e.g.*

"16943," "17001," etc., as shown in Table 1), followed by a "P" or "P2" suffix. The H4H and H2M prefixes on the antibody designations used herein indicate the particular Fc region isotype of the antibody. Thus, according to this nomenclature, an antibody may be referred to herein as, *e.g.*, "H4H16943P", etc., as the "H4H" designates the antibody has a human IgG4 Fc (all variable regions are fully human as denoted by the first 'H' in the antibody designation). As will be appreciated by a person of ordinary skill in the art, an antibody having a particular Fc isotype can be converted to an antibody with a different Fc isotype (*e.g.*, an antibody with a human IgG1 Fc can be converted to an antibody with a human IgG4, etc.), but in any event, the variable domains (including the CDRs) – which are indicated by the numerical identifiers shown in Table 1 – will remain the same, and the binding properties to antigen are expected to be identical or substantially similar regardless of the nature of the Fc domain.

[00254] Table 1c provides the amino acid sequence identifiers of the full length heavy and light chains of selected anti-Bet v 1 antibodies.

Table 1c: Heavy and Light Chain Amino Acid Sequence Identifiers

	SEQ ID NOs:	
Antibody Designation	**Heavy Chain**	**Light Chain**
H4H17038P2	316	317
H4H16987P	318	319
H4H16992P	320	321
H4H17082P2	322	323

Example 3: Antibody Binding to Bet v 1 as Determined by Surface Plasmon Resonance

[00255] Equilibrium dissociation constants (K_D) for natural Bet v 1 binding to purified anti-Bet v 1 monoclonal antibodies were determined using a real-time surface plasmon resonance biosensor (SPR-Biacore) on a Biacore 4000 instrument. All binding studies were performed in 10mM HEPES, 150mM NaCl, 3mM EDTA, and 0.05% v/v surfactant Tween-20, pH 7.4 (HBS-ET) running buffer at 25°C and 37°C. The Biacore CM5 sensor surface was first derivatized by amine coupling with a monoclonal mouse anti-human Fc antibody (GE, # BR-1008-39) to subsequently capture anti-Bet v 1 monoclonal antibodies. Different concentrations of natural Bet v 1 (Indoor, Cat# NA-BV1-1) or CHO produced recombinant Bet v 1 containing a S85A mutation with a C-terminal myc-myc hexahistidine tag (mutant Bet v 1-MMH; SEQ ID NO: 312) reagent were first prepared in HBS-ET running buffer

(100nM – 1.23nM; serially diluted by 3-fold) and were injected over anti-human Fc captured anti-Bet v 1 monoclonal antibody surface for 4 minutes at a flow rate of 30µL/minute, while the dissociation of monoclonal antibody bound Bet v 1 reagent was monitored for 10 minutes in HBS-ET running buffer. Association (k_a) and dissociation (k_d) rate constants were determined by fitting the real-time binding sensorgrams to a 1:1 binding model with mass transport limitation using Scrubber 2.0c curve-fitting software. Binding dissociation equilibrium constants (K_D) and dissociative half-lives (t½) were calculated from the kinetic rate constants as:

$$K_D = \frac{kd}{ka}, \quad \text{and} \quad t½ = \frac{\ln(2)}{kd}$$

[00256] Binding kinetics parameters for natural Bet v 1 and mutant Bet v 1-MMH to different anti-Bet v 1 monoclonal antibodies of the invention at 25°C and 37°C are shown in Table 2 through Table 5.

[00257] At 25°C, all of the anti-Bet v 1 monoclonal antibodies of the invention bound to natural Bet v 1 with K_D values ranging from 0.66nM to 13.5nM, as shown in Table 2. At 37°C, all of the anti-Bet v 1 monoclonal antibodies of the invention bound to natural Bet v 1 with K_D values ranging from 1.59nM to 27.9nM, as shown in Table 3. At both 25°C and 37°C the isotype control antibody did not demonstrate any measurable binding to natural Bet v 1.

[00258] At both 25°C and 37°C, 3 out of 20 anti-Bet v 1 monoclonal antibodies of the invention did not bind to mutant Bet v 1-MMH. At 25°C, 17 out of 20 anti-Bet v 1 monoclonal antibodies bound to mutant Bet v 1-MMH with K_D values ranging from 348pM to 43.8nM, as shown in Table 4. At 37°C, 17 out of 20 anti-Bet v 1 monoclonal antibodies of the invention bound to mutant Bet v 1-MMH with K_D values ranging from 655pM to 106nM, as shown in Table 5. At both 25°C and 37°C the isotype control antibody did not demonstrate any measurable binding to mutant Bet v 1-MMH.

Table 2: Binding kinetics parameters of natural Bet v 1 binding to Bet v 1 monoclonal antibodies at 25°C.

Antibody	mAb Capture Level (RU)	100nM natural Bet v 1 Bound (RU)	k_a (1/Ms)	k_d (1/s)	K_D (M)	t½ (min)

H4H16943P	346 ± 1.5	71	1.64E+05	2.30E-04	1.40E-09	50
H4H16946P	355 ± 1.8	74	2.05E+05	2.01E-04	9.82E-10	58
H4H16950P	357 ± 2.3	58	9.61E+04	5.03E-04	5.23E-09	23
H4H16960P	342 ± 2.2	57	4.22E+05	6.90E-04	1.64E-09	17
H4H16967P	332 ± 0.9	27	3.76E+04	1.49E-04	3.98E-09	77
H4H16971P	343 ± 0.5	57	2.40E+05	7.81E-04	3.26E-09	15
H4H16979P	295 ± 0.8	41	2.30E+05	2.78E-04	1.21E-09	42
H4H16987P	334 ± 0.5	61	4.10E+05	1.14E-03	2.77E-09	10
H4H16991P	313 ± 0.4	57	2.95E+05	3.12E-04	1.06E-09	37
H4H16992P	351 ± 0.7	64	3.73E+05	2.48E-04	6.65E-10	47
H4H17001P	352 ± 0.6	71	3.29E+05	3.29E-04	1.00E-09	35
H4H17015P	370 ± 0.7	68	1.84E+05	2.46E-04	1.34E-09	47
H4H17027P	340 ± 0.6	48	6.24E+04	2.70E-04	4.32E-09	43
H4H17028P	350 ± 0.7	63	2.81E+05	1.07E-03	3.79E-09	11
H4H17031P	335 ± 0.7	54	1.24E+05	1.68E-03	1.35E-08	6.8
H4H17033P	336 ± 0.4	61	3.94E+05	4.69E-04	1.19E-09	25
H4H17038P2	324 ± 0.9	64	2.77E+05	3.64E-04	1.32E-09	32
H4H17045P2	368 ± 0.9	69	1.22E+05	1.49E-04	1.22E-09	78
H4H17067P2	344 ± 0.5	58	1.13E+05	4.02E-04	3.56E-09	29
H4H17082P2	366 ± 0.6	72	5.45E+05	5.97E-04	1.09E-09	19
Isotype Control	345 ± 0.5	1	NB*	NB*	NB*	NB*

*NB indicates that no binding was observed under the current experimental conditions.

Table 3: Binding kinetics parameters of natural Bet v 1 binding to Bet v 1 monoclonal antibodies at 37°C.

Antibody	**mAb Capture Level (RU)**	**100nM natural Bet v 1 Bound (RU)**	**k_a (1/Ms)**	**k_d (1/s)**	**K_D (M)**	**t½ (min)**
H4H16943P	451 ± 2.7	88	2.60E+05	1.27E-03	4.89E-09	9.1
H4H16946P	469 ± 2.6	93	2.89E+05	6.01E-04	2.08E-09	19
H4H16950P	471 ± 2.1	76	1.41E+05	1.21E-03	8.57E-09	10
H4H16960P	422 ± 0.9	65	6.62E+05	1.68E-03	2.54E-09	6.8
H4H16967P	412 ± 1.9	45	5.04E+04	7.19E-04	1.43E-08	16
H4H16971P	433 ± 1.3	66	3.52E+05	2.44E-03	6.93E-09	4.7
H4H16979P	352 ± 1.3	52	3.42E+05	6.16E-04	1.80E-09	19
H4H16987P	436 ± 1.7	74	5.20E+05	4.77E-03	9.16E-09	2.4
H4H16991P	379 ± 1.0	66	5.00E+05	1.08E-03	2.16E-09	11

H4H16992P	436 ± 1.1	73	5.38E+05	8.53E-04	1.59E-09	14
H4H17001P	457 ± 0.8	87	4.85E+05	1.22E-03	2.52E-09	9.5
H4H17015P	464 ± 1.4	84	2.93E+05	7.92E-04	2.70E-09	15
H4H17027P	427 ± 0.9	67	9.81E+04	9.30E-04	9.48E-09	12
H4H17028P	435 ± 1.3	71	3.73E+05	2.90E-03	7.77E-09	3.9
H4H17031P	419 ± 1.8	63	4.85E+05	5.44E-03	2.79E-08	2.1
H4H17033P	417 ± 1.4	74	6.27E+05	1.19E-03	1.90E-09	10
H4H17038P2	406 ± 1.4	74	3.73E+05	1.62E-03	4.33E-09	7.1
H4H17045P2	465 ± 1.4	90	2.37E+05	4.41E-04	1.86E-09	26
H4H17067P2	440 ± 1.2	80	2.68E+05	1.47E-03	5.48E-09	7.9
H4H17082P2	453 ± 1.1	83	7.48E+05	1.82E-03	2.43E-09	6.3
Isotype Control	426 ± 1	1	NB*	NB*	NB*	NB*

*NB indicates that no binding was observed under the current experimental conditions.

Table 4: Binding kinetics parameters of mutant Bet v 1-MMH binding to Bet v 1 monoclonal antibodies at 25°C.

Antibody	**mAb Capture Level (RU)**	**100nM mutant Bet v 1-MMH Bound (RU)**	**k_a (1/Ms)**	**k_d (1/s)**	**K_D (M)**	**t½ (min)**
H4H16943P	344 ± 0.8	0	NB*	NB*	NB*	NB*
H4H16946P	354 ± 0.5	83	4.05E+05	1.41E-04	3.48E-10	82
H4H16950P	357 ± 0.6	70	1.51E+05	3.35E-04	2.21E-09	35
H4H16960P	343 ± 0.8	64	5.62E+05	4.43E-04	7.89E-10	26
H4H16967P	331 ± 0.3	0	NB	NB	NB	NB
H4H16971P	343 ± 0.5	58	4.07E+05	3.86E-03	9.48E-09	3.0
H4H16979P	293 ± 1.0	46	2.86E+05	2.30E-04	8.04E-10	50
H4H16987P	334 ± 0.4	46	4.90E+05	2.15E-02	4.38E-08	0.5
H4H16991P	312 ± 0.5	61	3.90E+05	2.87E-04	7.35E-10	40
H4H16992P	350 ± 0.4	70	4.59E+05	2.76E-04	6.01E-10	42
H4H17001P	351 ± 0.7	1	NB*	NB*	NB*	NB*
H4H17015P	368 ± 0.8	76	2.72E+05	2.81E-04	1.03E-09	41
H4H17027P	340 ± 0.4	63	1.10E+05	3.19E-04	2.90E-09	36
H4H17028P	349 ± 0.5	71	8.11E+05	6.93E-04	8.54E-10	17
H4H17031P	333 ± 0.5	63	1.87E+05	1.05E-03	5.61E-09	11
H4H17033P	336 ± 0.5	67	5.40E+05	4.15E-04	7.68E-10	28
H4H17038P2	324 ± 1	63	6.42E+05	6.41E-03	9.98E-09	1.8

H4H17045P2	368 ± 1.1	60	8.00E+04	4.98E-04	6.23E-09	23
H4H17067P2	344 ± 0.3	55	1.00E+05	1.17E-03	1.17E-08	9.9
H4H17082P2	366 ± 0.5	78	5.30E+05	6.12E-04	1.16E-09	19
Isotype Control	344 ± 0.8	1	NB*	NB*	NB*	NB*

*NB indicates that no binding was observed under the current experimental conditions.

Table 5: Binding kinetics parameters of mutant Bet v 1-MMH binding to Bet v 1 monoclonal antibodies at 37°C.

Antibody	mAb Capture Level (RU)	100nM mutant Bet v 1-MMH Bound (RU)	k_a (1/Ms)	k_d (1/s)	K_D (M)	t½ (min)
H4H16943P	441 ± 1.3	0	NB*	NB*	NB*	NB*
H4H16946P	459 ± 1.8	97	6.03E+05	3.95E-04	6.55E-10	29
H4H16950P	461 ± 1.2	83	2.15E+05	1.25E-03	5.81E-09	9.2
H4H16960P	417 ± 1.4	72	8.79E+05	1.77E-03	2.01E-09	6.5
H4H16967P	405 ± 0.8	-1	NB*	NB*	NB*	NB*
H4H16971P	427 ± 1.2	60	6.48E+05	1.20E-02	1.86E-08	1.0
H4H16979P	348 ± 0.7	56	4.62E+05	7.30E-04	1.58E-09	16
H4H16987P	429 ± 1.1	36	7.95E+05	8.47E-02	1.06E-07	0.14
H4H16991P	376 ± 0.7	67	7.17E+05	1.06E-03	1.48E-09	11
H4H16992P	432 ± 0.6	78	7.84E+05	8.85E-04	1.13E-09	13
H4H17001P	451 ± 0.8	2	NB*	NB*	NB*	NB*
H4H17015P	458 ± 1.1	89	4.45E+05	8.99E-04	2.02E-09	13
H4H17027P	421 ± 0.8	78	1.71E+05	1.16E-03	6.80E-09	9.9
H4H17028P	430 ± 0.8	77	1.01E+06	2.35E-03	2.32E-09	4.9
H4H17031P	413 ± 1.4	71	2.78E+05	4.06E-03	1.46E-08	2.8
H4H17033P	414 ± 0.8	79	8.83E+05	1.18E-03	1.34E-09	9.8
H4H17038P2	399 ± 0.9	56	8.33E+05	2.96E-02	3.56E-08	0.39
H4H17045P2	458 ± 1.2	84	1.62E+05	2.32E-03	1.43E-08	5.0
H4H17067P2	435 ± 0.7	76	2.53E+05	4.28E-03	1.69E-08	2.7
H4H17082P2	448 ± 1	89	8.21E+05	1.90E-03	2.31E-09	6.1
Isotype Control	421 ± 0.7	-2	NB*	NB*	NB*	NB*

*NB indicates that no binding was observed under the current experimental conditions.

Example 4: Antibody Binding to Related Allergens as Determined by Surface Plasmon Resonance

[00259] Equilibrium dissociation constants (K_D) for different related allergens binding to purified anti-Bet v 1 monoclonal antibodies were determined using a real-time surface plasmon resonance biosensor (SPR-Biacore) on a Biacore 4000 instrument. All binding studies were performed in 10mM HEPES, 150mM NaCl, 3mM EDTA, and 0.05% v/v surfactant Tween-20, pH 7.4 (HBS-ET) running buffer at 25°C. The Biacore CM5 sensor surface was first derivatized by amine coupling with a monoclonal mouse anti-human Fc antibody (GE, # BR-1008-39) to capture the anti-Bet v 1 monoclonal antibodies. Binding studies were performed on the following related allergens: Alder (Aln g 1, MyBiosource, Cat# MBS1041484), Apple (Mal d 1, MyBiosource, Cat# MBS1224919), Carrot (Dau c 1.2, MyBiosource, Cat# MBS1212920), Celery (Api g 1, MyBiosource, Cat# MBS1171376), Celery (Api g 2, MyBiosource, Cat# MBS1047880), European Hornbeam (Car b 1 isoform 1A & 1B, MyBiosource, Cat# MBS1200018), European Hornbeam (Car b 1 isoform 2, MyBiosource, Cat# MBS1043940), Hazel (Cor A 1, MyBiosource, Cat# MBS5304600), and White Oak (Que a 1, MyBiosource, Cat# MBS1258822). Different concentrations of the related allergens were prepared in HBS-ET running buffer (100nM – 6.25nM; serially diluted by 4-fold) and then were injected over anti-human Fc captured anti-Bet v 1 monoclonal antibody surface for 3 minutes at a flow rate of 30µL/minute, while the dissociation of monoclonal antibody bound allergens was monitored for 8 minutes in HBS-ET running buffer. Association (k_a) and dissociation (k_d) rate constants were determined by fitting the real-time binding sensorgrams to a 1:1 binding model with mass transport limitation using Scrubber 2.0c curve-fitting software. Binding dissociation equilibrium constants (K_D) and dissociative half-lives (t½) were calculated from the kinetic rate constants as:

$$K_D = \frac{\boldsymbol{kd}}{\boldsymbol{ka}}, \quad \text{and} \quad t½ = \frac{\mathbf{ln(2)}}{\boldsymbol{kd}}$$

[00260] Binding kinetics parameters for related allergens to different anti-Bet v 1 monoclonal antibodies of the invention at 25°C are shown in Table 6 through Table 11.

[00261] As shown in Table 6 at 25°C, nine of the 20 anti-Bet v 1 antibodies of the invention demonstrated measurable binding to Aln g 1 with K_D values ranging from 1.03 nM to 175 nM. The other 11 antibodies did not demonstrate any measurable binding to Aln g 1 under the tested conditions.

[00262] As shown in Table 7 at 25°C, two of the 20 anti-Bet v 1 antibodies of the invention demonstrated measurable binding to Mal d 1 with K_D values of 29.8 nM and 494

nM. The other 18 antibodies did not demonstrate any measurable binding to Mal d 1 under the tested conditions.

[00263] As shown in Table 8 at 25°C, one of the anti-Bet v 1 antibodies of the invention demonstrated measurable binding to Api g 1 with a K_D value of 167 nM. The other 19 antibodies did not demonstrate any measurable binding to Api g 1 under the tested conditions.

[00264] As shown in Table 9 at 25°C, eight of the 20 of the anti-Bet v 1 antibodies of the invention demonstrated measurable binding to Car b 1 isoform 1A & 1B with K_D values ranging from 1.2 nM to 380 nM. The other 12 antibodies did not demonstrate any measurable binding to Car b 1 isoform 1A & 1B under the tested conditions.

[00265] As shown in Table 10 at 25°C, 14 of the 20 of the anti-Bet v 1 antibodies of the invention demonstrated measurable binding to Car b 1 isoform 2 with K_D values ranging from 335 pM to 564 nM. The other 6 antibodies did not demonstrate any measurable binding to Car b 1 isoform 2 under the tested conditions.

[00266] As shown in Table 11 at 25°C, one of the anti-Bet v 1 antibodies of the invention demonstrated measurable binding to Cor A 1 with a K_D value of 396 nM. The other 19 antibodies did not demonstrate any measurable binding to Cor A 1 under the tested conditions.

[00267] None of the antibodies of the invention demonstrated measurable binding to Dau c 1.2, Api g 2, or Que a 1 under the conditions tested (data not shown). The isotype control antibody did not demonstrate any measurable binding to any of the allergens tested.

Table 6: Binding kinetics parameters of Alder (Aln g1) binding to Bet v 1 monoclonal antibodies at 25°C.

Antibody	mAb Capture Level (RU)	100nM Analyte Bound (RU)	k_a (1/Ms)	k_d (1/s)	K_D (M)	t½ (min)
H4H16943P	675 ± 0.9	1	NB*	NB*	NB*	NB*
H4H16946P	668 ± 1.2	2	NB*	NB*	NB*	NB*
H4H16950P	634 ± 1.7	15	9.12E+04	1.60E-02	1.75E-07	0.7
H4H16960P	681 ± 2.1	29	2.26E+05	3.32E-02	1.47E-07	0.3
H4H16967P	666 ± 3.1	0	NB*	NB*	NB*	NB*
H4H16971P	668 ± 2.1	41	9.30E+04	1.18E-02	1.26E-07	1.0

H4H16979P	545 ± 0.4	0	NB*	NB*	NB*	NB*
H4H16987P	667 ± 1.6	139	2.21E+05	8.70E-04	3.94E-09	13
H4H16991P	608 ± 0.4	3	NB*	NB*	NB*	NB*
H4H16992P	653 ± 1.3	5	NB*	NB*	NB*	NB*
H4H17001P	630 ± 1.6	49	2.64E+05	2.78E-02	1.05E-07	0.4
H4H17015P	745 ± 3	8	NB*	NB*	NB*	NB*
H4H17027P	772 ± 0.4	9	9.29E+04	6.43E-03	6.92E-08	1.8
H4H17028P	708 ± 1.5	16	5.17E+04	1.90E-03	3.67E-08	6.1
H4H17031P	727 ± 1.3	59	5.29E+04	2.38E-03	4.50E-08	4.8
H4H17033P	649 ± 0.2	3	NB*	NB*	NB*	NB*
H4H17038P2	660 ± 1.3	2	NB*	NB*	NB*	NB*
H4H17045P2	746 ± 1.2	0	NB*	NB*	NB*	NB*
H4H17067P2	617 ± 2.2	2	NB*	NB*	NB*	NB*
H4H17082P2	662 ± 3.6	132	3.12E+05	3.23E-04	1.03E-09	36
Isotype Control	686 ± 1.3	0	NB*	NB*	NB*	NB*

*NB indicates that no binding was observed under the current experimental conditions.

Table 7: Binding kinetics parameters of Apple (Mal d 1) binding to Bet v 1 monoclonal antibodies at 25°C.

Antibody	mAb Capture Level (RU)	100nM Analyte Bound (RU)	k_a (1/Ms)	k_d (1/s)	K_D (M)	t½ (min)
H4H16943P	676 ± 0.7	-1	NB*	NB*	NB*	NB*
H4H16946P	668 ± 2.2	0	NB*	NB*	NB*	NB*
H4H16950P	635 ± 1.9	-1	NB*	NB*	NB*	NB*
H4H16960P	690 ± 8.2	1	NB*	NB*	NB*	NB*
H4H16967P	671 ± 3.2	-2	NB*	NB*	NB*	NB*
H4H16971P	667 ± 3.4	25	1.61E+05	7.95E-02	4.94E-07	0.2
H4H16979P	545 ± 0.5	1	NB*	NB*	NB*	NB*
H4H16987P	668 ± 0.8	2	NB*	NB*	NB*	NB*
H4H16991P	608 ± 1.4	0	NB*	NB*	NB*	NB*
H4H16992P	652 ± 0.8	3	NB*	NB*	NB*	NB*
H4H17001P	626 ± 0.8	0	NB*	NB*	NB*	NB*
H4H17015P	741 ± 2.6	0	NB*	NB*	NB*	NB*
H4H17027P	767 ± 1.4	0	NB*	NB*	NB*	NB*
H4H17028P	704 ± 2.3	1	NB*	NB*	NB*	NB*
H4H17031P	727 ± 1.6	0	NB*	NB*	NB*	NB*
H4H17033P	650 ± 1.6	1	NB*	NB*	NB*	NB*

H4H17038P2	658 ± 1.5	-1	NB*	NB*	NB*	NB*
H4H17045P2	747 ± 1.3	-1	NB*	NB*	NB*	NB*
H4H17067P2	616 ± 2	-1	NB*	NB*	NB*	NB*
H4H17082P2	662 ± 1.9	112	1.25E+06	3.74E-02	2.98E-08	0.3
Isotype Control	686 ± 1.1	0	NB*	NB*	NB*	NB*

*NB indicates that no binding was observed under the current experimental conditions.

Table 8: Binding kinetics parameters of Celery (Api g 1) binding to Bet v 1 monoclonal antibodies at 25°C.

Antibody	mAb Capture Level (RU)	100nM Analyte Bound (RU)	k_a (1/Ms)	k_d (1/s)	K_D (M)	t½ (min)
H4H16943P	674 ± 0.7	0	NB*	NB*	NB*	NB*
H4H16946P	666 ± 0.4	1	NB*	NB*	NB*	NB*
H4H16950P	632 ± 3	0	NB*	NB*	NB*	NB*
H4H16960P	684 ± 3.6	0	NB*	NB*	NB*	NB*
H4H16967P	668 ± 4.2	-1	NB*	NB*	NB*	NB*
H4H16971P	666 ± 0.7	0	NB*	NB*	NB*	NB*
H4H16979P	546 ± 1.1	0	NB*	NB*	NB*	NB*
H4H16987P	668 ± 0.8	1	NB*	NB*	NB*	NB*
H4H16991P	607 ± 1.3	0	NB*	NB*	NB*	NB*
H4H16992P	651 ± 2.9	1	NB*	NB*	NB*	NB*
H4H17001P	625 ± 1.3	-1	NB*	NB*	NB*	NB*
H4H17015P	740 ± 1.5	0	NB*	NB*	NB*	NB*
H4H17027P	765 ± 1.1	0	NB*	NB*	NB*	NB*
H4H17028P	705 ± 2.2	1	NB*	NB*	NB*	NB*
H4H17031P	727 ± 1.3	0	NB*	NB*	NB*	NB*
H4H17033P	648 ± 0.3	39	4.75E+05	7.91E-02	1.67E-07	0.2
H4H17038P2	659 ± 0.6	-1	NB*	NB*	NB*	NB*
H4H17045P2	747 ± 0.5	0	NB*	NB*	NB*	NB*
H4H17067P2	613 ± 0.6	0	NB*	NB*	NB*	NB*
H4H17082P2	660 ± 3.1	0	NB*	NB*	NB*	NB*
Isotype Control	684 ± 3.1	-1	NB*	NB*	NB*	NB*

*NB indicates that no binding was observed under the current experimental conditions.

Table 9: Binding kinetics parameters of European Hornbeam (Car b 1 isoform 1A & 1B) binding to Bet v 1 monoclonal antibodies at 25°C.

Antibody	mAb Capture Level (RU)	100nM Analyte Bound (RU)	k_a (1/Ms)	k_d (1/s)	K_D (M)	t½ (min)
H4H16943P	674 ± 1	26	1.52E+05	5.78E-02	3.80E-07	0.2
H4H16946P	667 ± 1.6	63	1.43E+05	2.40E-02	1.68E-07	0.5
H4H16950P	633 ± 1.6	-1	NB*	NB*	NB*	NB*
H4H16960P	687 ± 0.8	4	NB*	NB*	NB*	NB*
H4H16967P	666 ± 3.3	-1	NB*	NB*	NB*	NB*
H4H16971P	669 ± 4.6	1	NB*	NB*	NB*	NB*
H4H16979P	545 ± 0.4	1	NB*	NB*	NB*	NB*
H4H16987P	668 ± 0.3	0	NB*	NB*	NB*	NB*
H4H16991P	608 ± 1.8	1	NB*	NB*	NB*	NB*
H4H16992P	653 ± 0.6	161	2.81E+05	3.37E-04	1.20E-09	34
H4H17001P	626 ± 1	0	NB*	NB*	NB*	NB*
H4H17015P	742 ± 1.8	0	NB*	NB*	NB*	NB*
H4H17027P	767 ± 0.3	41	3.14E+04	6.73E-03	2.14E-07	1.7
H4H17028P	705 ± 0.7	159	2.10E+05	5.11E-04	2.43E-09	23
H4H17031P	726 ± 3.2	126	8.04E+04	1.11E-03	1.38E-08	10
H4H17033P	650 ± 1.3	0	NB*	NB*	NB*	NB*
H4H17038P2	659 ± 0.9	105	1.51E+05	6.23E-03	4.14E-08	1.9
H4H17045P2	748 ± 1	5	NB*	NB*	NB*	NB*
H4H17067P2	616 ± 1	0	NB*	NB*	NB*	NB*
H4H17082P2	664 ± 1.6	69	3.90E+05	3.53E-02	9.05E-08	0.3
Isotype Control	686 ± 0.7	0	NB*	NB*	NB*	NB*

*NB indicates that no binding was observed under the current experimental conditions.

Table 10: Binding kinetics parameters of European Hornbeam (Car b1 isoform 2) binding to Bet v 1 monoclonal antibodies at 25°C.

Antibody	mAb Capture Level (RU)	100nM Analyte Bound (RU)	k_a (1/Ms)	k_d (1/s)	K_D (M)	t½ (min)
H4H16943P	675 ± 1.6	183	1.11E+06	3.71E-04	3.35E-10	31
H4H16946P	666 ± 0.7	63	7.69E+04	1.38E-02	1.79E-07	0.8
H4H16950P	633 ± 3	0	NB*	NB*	NB*	NB*
H4H16960P	682 ± 4.5	1	NB*	NB*	NB*	NB*
H4H16967P	663 ± 5.4	0	NB*	NB*	NB*	NB*

H4H16971P	668 ± 4.1	23	2.59E+05	1.46E-01	5.64E-07	0
H4H16979P	547 ± 1.1	114	9.71E+05	2.41E-03	2.48E-09	4.8
H4H16987P	667 ± 1.3	153	1.01E+06	5.61E-03	5.56E-09	2.1
H4H16991P	607 ± 3.4	93	1.07E+06	4.04E-02	3.78E-08	0.3
H4H16992P	652 ± 0.6	156	1.40E+06	8.61E-04	6.17E-10	13
H4H17001P	625 ± 1.1	157	2.03E+06	3.20E-03	1.58E-09	3.6
H4H17015P	741 ± 1.6	2	NB*	NB*	NB*	NB*
H4H17027P	765 ± 1.8	42	5.84E+04	5.77E-03	9.89E-08	2.0
H4H17028P	703 ± 4.1	95	9.71E+04	4.37E-03	4.50E-08	2.6
H4H17031P	727 ± 1.2	160	3.95E+05	5.17E-03	1.31E-08	2.2
H4H17033P	650 ± 1.2	111	1.34E+06	4.47E-02	3.34E-08	0.3
H4H17038P2	660 ± 1.6	73	1.28E+05	6.48E-03	5.05E-08	1.8
H4H17045P2	747 ± 1.2	5	NB*	NB*	NB*	NB*
H4H17067P2	616 ± 1	1	NB*	NB*	NB*	NB*
H4H17082P2	661 ± 2	166	2.18E+06	1.24E-03	5.67E-10	9.3
Isotype Control	685 ± 1.2	0	NB*	NB*	NB*	NB*

*NB indicates that no binding was observed under the current experimental conditions.

Table 11: Binding kinetics parameters of Hazel (Cor A 1) binding to Bet v 1 monoclonal antibodies at 25°C.

Antibody	mAb Capture Level (RU)	100nM Analyte Bound (RU)	k_a (1/Ms)	k_d (1/s)	K_D (M)	t½ (min)
H4H16943P	673 ± 0.4	0	NB*	NB*	NB*	NB*
H4H16946P	665 ± 0.6	-1	NB*	NB*	NB*	NB*
H4H16950P	635 ± 3.3	0	NB*	NB*	NB*	NB*
H4H16960P	687 ± 7	0	NB*	NB*	NB*	NB*
H4H16967P	668 ± 1.7	0	NB*	NB*	NB*	NB*
H4H16971P	666 ± 5.8	0	NB*	NB*	NB*	NB*
H4H16979P	546 ± 1.1	0	NB*	NB*	NB*	NB*
H4H16987P	668 ± 0.7	0	NB*	NB*	NB*	NB*
H4H16991P	607 ± 1.3	0	NB*	NB*	NB*	NB*
H4H16992P	652 ± 1.6	0	NB*	NB*	NB*	NB*
H4H17001P	626 ± 0.4	0	NB*	NB*	NB*	NB*
H4H17015P	740 ± 0.7	1	NB*	NB*	NB*	NB*
H4H17027P	766 ± 2.8	0	NB*	NB*	NB*	NB*
H4H17028P	704 ± 1.3	0	NB*	NB*	NB*	NB*
H4H17031P	727 ± 1.2	0	NB*	NB*	NB*	NB*

H4H17033P	649 ± 1.5	0	NB*	NB*	NB*	NB*
H4H17038P2	659 ± 0.1	0	NB*	NB*	NB*	NB*
H4H17045P2	748 ± 0.8	0	NB*	NB*	NB*	NB*
H4H17067P2	614 ± 0.7	-1	NB*	NB*	NB*	NB*
H4H17082P2	661 ± 0.8	20	1.06E+05	4.18E-02	3.96E-07	0.3
Isotype Control	685 ± 0.5	1	NB*	NB*	NB*	NB*

*NB indicates that no binding was observed under the current experimental conditions.

Example 5: Blocking Bet v 1 binding to allergen specific IgE by anti-Bet v 1 IgG antibodies

[00268] The ability of single anti-Bet v 1 antibodies of the invention or combinations of anti-Bet v 1 antibodies of the invention to block Bet v 1 binding to plate-captured IgE from allergic human donor plasma/sera was determined using an ELISA. Antibodies were tested either alone or in polyclonal mixes. For the assay, microtiter plates were coated overnight at 4°C with human FcεR1α (the high affinity receptor for IgE) extracellular domain protein that was produced with a C-terminal mouse Fc tag (hFcεR1α-mFc; SEQ ID NO: 313). Plates were then blocked with 0.5% BSA (w/v) for 1 hour at room temperature (RT). Plasma from allergic donors was diluted and total IgE was then captured over the receptor-coated surface. A constant amount of 0.1nM of biotin labeled natural Bet v 1 (Indoor Biotechnologies, # NA-BV1-1) was pre-mixed with anti-Bet v 1 antibodies, at a single concentration of 1 µg/mL or in serial dilutions starting from either 10 µg/mL or 1 µg/mL of each antibody and incubated for 1 hour at RT to allow Bet v 1-antibody interaction to reach equilibrium. The antibody-Bet v 1 mixture was then added to the IgE-coated plate for 1 hour. Plates were subsequently washed and the amount of natural Bet v 1 bound to plate was detected using streptavidin conjugated to horseradish peroxidase (Thermo Scientific, # N200/QJ223091) at a 1:10,000 dilution and incubated for 1 hour at RT. Plates were then washed with PBS-T in between each step of the ELISA protocol described above. To develop the colorimetric reaction, TMB/H_2O_2 substrate (BD Pharmingen Reagent A #51-2602KC + Reagent B, #51-2607KC) was added to the plates and incubated for 20 minutes at RT. The reaction was stopped using 2 N sulfuric acid (H_2SO_4; VWR, # BDH3500-1). The absorbance was subsequently measured on a spectrophotometer (Victor, Perkin Elmer) at 450 nm. The percent blocking was calculated using the highest antibody concentration used in each assay as described below.

$$\text{Percent blocking} = \frac{(A_{450} \text{ with no antibody}) - (A_{450} \text{ at highest antibody concentration})}{(A_{450} \text{ with no antibody})} \times 100$$

[00269] Twenty anti-Bet v 1 antibodies were tested as single antibodies for their ability to block Bet v 1 binding to plate-captured IgE from allergic human donor plasma using the ELISA described. Individual monoclonal antibodies were able to partially block IgE binding to Bet v 1 by 8.5-64%, which underlines the polyclonality of the IgEs. Seven antibodies showed blocking ranging from 36 - 64% at the highest antibody concentration tested of 10 μg/mL, as shown in Table 12.

[00270] Four anti-Bet v 1 antibodies, H4H17082P2, H4H17038P2, H4H16987P, and H4H16992P were tested in a single point blocking assay. A combination of H4H17082P2 and H4H16992P demonstrated greater than 90% blocking in seven out of ten IgE donors. Three and four monoclonal antibody combinations demonstrated similar results and did not appear to add any additional blocking effect as compared to the two-antibody combination of H4H17082P2 and H4H16992P, as shown in Table 13.

[00271] The four monoclonal antibodies, H4H17082P2, H4H17038P2, H4H16987P, and H4H16992P, were subsequently tested as single and 2, 3 and 4 monoclonal antibody combinations in dose response blocking assay with 3 donor IgE samples. The results showed that the anti-Bet v 1 two monoclonal antibody combination of H4H17082P2 and H4H16992P blocked Bet v 1 binding to allergen specific IgE greater than 90% and close to baseline in 3 donors, as shown in Table 14. The tested 3- and 4- antibody combinations showed similar breadth and potency of blocking activity. As positive control, purified mouse anti-Bet v 1 polyclonal IgG demonstrated >90% blocking.

Table 12: Anti-Bet v 1 antibodies blocking Bet v 1 binding to allergen specific IgE

Donor ID:	**23397-PB**	**24606-AB**
Antibodies	**% Blocking of Bet v 1 binding to captured IgE**	
H4H17082P2 MAB2	56.6	60.3
H4H16971P	35.4	12.8
H4H17027P	23.0	28.4
H4H17028P	19.7	16.6
H4H16946P	27.6	22.8
H4H17038P2 MAB3	49.0	55.3
H4H16950P	32.3	20.7
H4H16987P MAB4	15.2	12.8
H4H17045P2	27.4	27.2
H4H17067P2	25.7	22.2

H4H16967P	21.8	23.5
H4H17015P	41.8	63.4
H4H16979P	33.6	12.9
H4H16991P	30.0	32.6
H4H17033P	51.8	49.0
H4H16992 MAB1	36.7	64.4
H4H16960P	8.5	17.6
H4H17031	16.7	20.5
H4H17001P	47.2	52.7
H4H16943P	47.7	52.5

Allergy donor plasma was diluted 1:50 for these assays.

Table 13: Single antibodies and antibody combinations blocking Bet v 1 binding to allergen specific IgE

Donor ID:	**23658-MD**	**23939-MH**	**23035-BL**	**25414-CW**	**25340-RR**	**25299-RJ**	**25609-MS**	**26532-CC**	**29718-MW**	**22627-MN**
Antibodies	**Percent Blocking (at 1 µg/mL each antibody)**									
H4H17082P2 MAB2	62	79	52	38	81	66	51	74	49	61
H4H17038P2 MAB3	24	17	36	23	28	24	17	23	14	23
H4H16987P MAB4	27	16	-46	-4	15	9	16	4	13	12
H4H16992P MAB1	44	53	43	53	67	70	89	80	82	62
H4H17082P2 + H4H17038P2	70	85	73	57	90	78	65	83	60	79
H4H17082P2 + H4H16987P	74	88	21	45	84	69	65	75	61	76
H4H17082P2 + H4H16992P	79	93	72	77	91	91	98	94	94	96
H4H17038P2 + H4H16987P	47	31	16	28	41	29	33	29	28	47
H4H17038P2 + H4H16992P	58	62	51	77	83	75	93	87	87	77

H4H16987P + H4H16992P	61	61	-6	63	75	69	94	81	89	64
H4H17082P2 + H4H17038P2 + H4H16987P	78	88	39	63	91	79	72	83	68	85
H4H17082P2 + H4H17038P2 + H4H16992P	83	92	65	91	96	89	98	94	94	90
H4H17082P2 + H4H16987P + H4H16992P	83	91	16	85	91	79	96	90	95	78
H4H17038P2 + H4H16987P + H4H16992P	71	69	3	82	88	71	95	86	93	76
H4H17082P2 + H4H17038P2 + H4H16987P + H4H16992P	86	93	44	89	95	84	98	94	97	87
Biotinylated Bet v 1 (no antibody) at 0.1nM	0	0	0	0	0	0	0	0	0	0
Isotype control	-3	-2	-5	-4	-1	-4	-2	-4	-2	-3

Allergy donor plasma was normalized to either to 1:20 (6 donors), 1:10 (3 donors) or 1:9 (1 donor) Bet v 1 specific IgE titer and then diluted 1:50 for this assay.

Table 14: Antibody combinations blocking Bet v 1 binding to allergen specific IgE

Donor ID:	**23939-MH**	**25340-RR**	**25609-MS**
Antibody	**Percent Blocking (at 1 µg/mL each antibody)**		
H4H17082P2	82.9	82.7	56.4
H4H17038P2	20.2	23.2	22.8
H4H16987P	19.6	11.1	21.6
H4H16992P	63.3	70.2	86.9

H4H17082P2 + H4H16992P	94.8	93.8	96.5
H4H17082P2 + H4H17038P2 + H4H16992P	93.4	96.4	95.2
H4H17082P2 + H4H16987P + H4H16992P	91.5	93.1	94.2
H4H17082P2 + H4H17038P2 + H4H16987P + H4H16992P	92.6	95.4	95.7
Isotype control	16.8	10.6	8.8
Purified anti-Bet v 1 mouse IgG at 333.3nM	92.7	93.9	94.6

Example 6: Epitope Mapping of Anti-Bet v 1 Antibodies Binding to Bet v 1 by Hydrogen Deuterium (H/D) Exchange

[00272] To determine the amino acid residues of Bet v 1 [(amino acids M1-N160 of Uniprot P15494] with which H4H16992P2, H4H17082P2, H4H17038P2, and H4H16987P interact, a H/D exchange epitope mapping with mass spectrometry study was performed. A general description of the H/D exchange method is set forth in e.g., Ehring (1999) *Analytical Biochemistry* 267(2):252-259; and Engen and Smith (2001) *Anal. Chem.* 73:256A-265A.

[00273] The HDX-MS experiments were performed on an integrated Waters HDX/MS platform, consisting of a Leaptec HDX PAL system for the deuterium labeling, a Waters Acquity M-Class (Auxiliary solvent manager) for the sample digestion and loading, a Waters Acquity M-Class (μBinary solvent manager) for the analytical column gradient, and Synapt G2-Si mass spectrometer for peptic peptide mass measurement.

[00274] The labeling solution was prepared in 10 mM PBS buffer in D_2O at pD 7.0 (equivalent to pH 6.6). For deuterium labeling, 3.8 μL of natural Bet v 1 (Indoor Biotech, Catalog # NA-BV1-1, 28 pmol/μL), Bet v 1 premixed with each antibody, or the mixture of all 4 anti-Bet v 1 antibodies in a 1:1 molar ratio was incubated with 56.2 μL D_2O labeling solution for various time-points (e.g., Undeuterated control = 0 second, labeled for 1 minute, 5 minutes, 10 minutes and 20 minutes). The deuteration was quenched by transferring 50 μL of the sample to 50 μL of pre-chilled 0.2 M TCEP, 6 M guanidine chloride in 100 mM phosphate buffer, pH 2.5 (quench buffer) and the mixed sample was incubated at 1.0 °C for 2 minutes. The quenched sample was then injected into a Waters HDX Manager for online

pepsin/protease XIII digestion. The digested peptides were trapped onto an ACQUITY UPLC BEH C18 1.7-μm, 2.1 × 5 mm VanGuard pre-column at 0°C and eluted to an analytical column ACQUITY UPLC BEH C18 1.7-μm, 1.0 × 50 mm for a 9-minute gradient separation of 5%-40% B (mobile phase A: 0.1% formic acid in water, mobile phase B: 0.1% formic acid in acetonitrile). The mass spectrometer was set at a cone voltage of 37 V, scan time of 0.5 seconds, and mass/charge range of 50-1700 Th.

[00275] For the identification of the peptides from Bet v 1, LC- MS^E data from undeuterated sample were processed and searched against the database including Bet v 1and its randomized sequence via Waters ProteinLynx Global Server (PLGS) software. The identified peptides were imported to DynamX software and filtered by two criteria: 1) minimum products per amino acid: 0.3, and 2) replication file threshold: 3. DynamX software then automatically determined deuterium uptake of each peptide based on retention time and high mass accuracy (<10ppm) across multiple time points with 3 replicates at each time.

[00276] Using the online pepsin/protease XIII column coupled with MS^E data acquisition, a total of 36 peptides from Bet v 1 were reproducibly identified in the absence or presence of the antibody, representing 91.2% sequence coverage. Peptides with significantly reduced deuteration uptake when bound to H4H16992P2, H4H17082P2, H4H17038P2, H4H16987P and 4 antibody combinations are illustrated in Figures 1 through 4 and 5, respectively. The recorded peptide mass corresponds to the average value of the centroid MH^+ mass from three replicates of Bet v 1 in complex with anti-Bet v 1 antibody or antibodies.

[00277] As shown in Figure 1, the peptides corresponding to amino acids 23-43 (FILDGDNLFPKVAPQAISSVE, SEQ ID NO: 307) had a slower deuteration rate in the presence of H4H16992P.

[00278] As shown in Figure 2, the peptides corresponding to amino acids 44-56 (NIEGNGGPGTIKK, SEQ ID NO: 308) had a slower deuteration rate in the presence of H4H17082P.

[00279] As shown in Figure 3, the peptides corresponding to amino acids 2-19 (GVFNYETETTSVIPAARL, SEQ ID NO: 309) had a slower deuteration rate in the presence of H4H17038P2.

[00280] As shown in Figure 4, the peptides corresponding to amino acids 57-70 (ISFPEGFPFKYVKD, SEQ ID NO: 310) and 81-96 (KYNYSVIEGGPIGDTL, SEQ ID NO: 315) had a slower deuteration rate in the presence of H4H16987P.

[00281] As shown in Figure 5, the peptides corresponding to amino acids 23-43 (FILDGDNLFPKVAPQAISSVE, SEQ ID NO: 307), amino acids 44-56 (NIEGNGGPGTIKK, SEQ ID NO: 308), 2-19 (GVFNYETETTSVIPAARL, SEQ ID NO: 309), amino acids 57-70 (ISFPEGFPFKYVKD, SEQ ID NO: 310) and 81-96 (KYNYSVIEGGPIGDTL, SEQ ID NO: 315) had slower deuteration rates in the presence of the 4 anti-Bet v 1 antibody combination (H4H16992P, H4H17082P, H4H17038P2 and H4H16987P).

[00282] In addition, a modest level of protection was observed for peptide 23-43 in the presence of H4H17082P, H4H17038P2 and H4H16987P, identifying that this region could represent a secondary epitope for these monoclonal antibodies.

Example 7: Effect of anti-Bet v 1 antibodies in the passive cutaneous anaphylaxis (PCA) *in vivo* model

[00283] To determine the efficacy of anti-Bet v 1 antibodies of the invention for blocking allergen induced mast cell degranulation the passive cutaneous anaphylaxis (PCA) *in vivo* model was used. This model involves intradermal injection of an allergen-specific antiserum into a local area on the skin followed by intravenous injection of an antigen along with a dye. The allergic reaction causes capillary dilatation and increased vascular permeability at the site of sensitization, resulting in preferential accumulation of dye at this site. The dye can be extracted from the tissue and quantitated spectrophotometrically. Dye extravasation into tissue sensitized with test antiserum can then be compared to extravasation into tissue sensitized with a non-relevant antiserum.

[00284] Antisera were generated for use in the assay by immunizing Balb/c mice with 5μg of natural Bet v 1 protein (Indoor Biotechnologies, # NA-BV1-1) in a solution of 1mg/mL of alum in 1X phosphate buffered saline (PBS) on day 0. One week later (day 7), sensitized mice were boosted with 5μg natural Bet v 1 protein in a solution of 1mg/mL alum in 1X PBS. Two weeks after the boost, mice were subjected to an intranasal airway challenge with 0.5 μg of natural Bet v 1 protein in 20μL PBS on days 21, 24 and 28. Mice were then sacrificed on day 31 and serum was collected. The total IgE concentration in the isolated antisera was determined using an OptEIA™ ELISA kit (BD Biosciences, #555248) according to the manufacturer's instructions. The final concentration of Bet v 1 antisera was diluted to 2600 ng/mL of IgE in PBS.

[00285] Antisera used as a negative control in the assay was generated by immunizing Balb/c mice with 5μg natural Fel d 1 protein purified from cat hair extract (Indoor

Biotechnologies, # LTN-FD1-1) in a solution of 1mg/mL of alum in PBS on day 0. Mice were boosted with 5μg Fel d 1 protein in a solution of 1mg/mL alum in PBS on days 14 and 21. One week after the final boost (day 28), mice were sacrificed and serum was collected. The total IgE concentration in the isolated antisera was determined using an OptEIA™ ELISA kit (BD Biosciences, #555248) according to the manufacturer's instructions. The final concentration of antisera was diluted to 2500 ng/mL of IgE in PBS.

[00286] For the PCA assays, groups of Balb/c mice (n≥5 per experiment) were first subcutaneously injected with either an isotype control antibody, an anti-Bet v 1 antibody, or a combination of anti-Bet v 1 antibodies at a dose of 1mg/kg (total antibody dose). Three days after antibody administration, 10μL of either 1.5 ng Bet v 1 antiserum or 3 ng negative control anti-serum were injected into the right and left ears of mice in each group, respectively. Twenty-four hours after the local administration of allergen-specific antisera, mice were challenged by intravenous injection (100 μL per mouse) of a solution of 1 μg/mL of natural Bet v 1 dissolved in PBS containing 0.5% (w/v) Evan's blue dye (Sigma Aldrich, # E2129). One hour after antigen challenge, mice were sacrificed, their ears were excised, placed in 1 mL formamide, and subsequently incubated for 3 days from 50-56°C to extract the Evan's blue dye. The ear tissue was then removed from the formamide, blotted to remove excess liquid and weighed. Two-hundred microliter aliquots of each formamide extract were transferred to 96 well plates in duplicate and their absorbance was then measured at 620nm. The optical density measured was converted to Evan's blue dye concentration using a standard curve and represented as ng of Evan's blue dye per mg tissue. Mean values ± the standard deviation are shown in Table 15 for each group. Mean difference as compared to isotype control was calculated using Bonferroni's multiple comparisons test in GraphPad Prism.

[00287] As shown in Table 15, in the first study, the single anti-Bet v 1 antibody, H4H17082P2, did not demonstrate a significant reduction of dye extravasation compared to isotype control. In contrast in Study 2, the combination of two anti-Bet v 1 antibodies of the invention (H4H16992P and H4H17082P2) and the combination of four anti-Bet v 1 antibodies of the invention (H4H16992P, H4H17082P2, H4H17038P2, and H4H16987P) demonstrated significant reductions of dye extravasation as compared to the isotype control treatment, with reductions of 35.26 and 36.49 ng/mg respectively. Similarly, in Study 3 the combination of two anti-Bet v 1 antibodies of the invention (H4H16992P and H4H17082P2) again demonstrated significant reductions of dye extravasation as compared to the isotype control treatment, with a reduction of 41.09 ng/mg. As was previously demonstrated in Study

1, in Study 3 the single anti-Bet v 1 antibody, H4H17082P2, did not demonstrate a significant reduction of dye extravasation compared to isotype control. However, another single antibody, H4H16992P, demonstrated a significant reduction of dye extravasation compared to isotype control, with a reduction of 25.86ng/mg. From the studies conducted the single antibody H4H16992P, the two-antibody combination of H4H17082P2 + H4H16992P, as well as the four-antibody combination of H4H17082P2 + H4H16992P + H4H17038P2 + H4H16987P were able to block mast cell degranulation as indicated by a significant reduction of dye extravasation compared to isotype control in the passive cutaneous anaphylaxis *in vivo* model as determined by two-way ANOVA with Bonferroni's post test. The H4H17082P2 antibody alone was not able to block mast cell degranulation as indicated by an increase in dye extravasation compared to isotype in two of the studies conducted. The number of mice used per group (n) is noted within parentheses in the table.

Table 15: Effect of anti-Bet v 1 antibodies in the passive cutaneous anaphylaxis *in vivo* model.

Treatment Group	Negative control allergen (ng Evans Blue/mg tissue ±SD)	Mean Difference Compared to Isotype Control	Bet v 1 (ng Evans Blue/mg tissue ±SD)	Mean Difference Compared to Isotype Control
Study 1				
H4H17082P2 (n=8)	2.1±0.9	-0.31	46.6 ±17.3	7.5
Study 2				
H4H17082P2 + H4H16992P (n=10)	6.3±3.8	1.807	8.3±7.7	**-35.26 (****)**
H4H17082P2 + H4H16992P + H4H17038P2 + H4H16987P (n=10)	7.6±5.5	3.090	7.1±4.1	**-36.49 (****)**
Study 3				
H4H17082P2 (n=5)	6.5±1.4	-0.311	89.4±28.3	27.37 (*)
H4H16992P (n=5)	6.4±2.1	-0.324	36.2±14	**-25.86 (*)**
H4H17082P2 + H4H16992P (n=5)	3.6±.31	-3.118	21±9.6	**-41.09 (***)**

1mg/kg total antibody concentration used for all antibody treatment groups

*P≤.05, ***P≤.001, ***P≤.0001

n= number of mice in each group

Example 8: Effect of anti-Bet v 1 antibodies against three different birch pollen extracts in the passive cutaneous anaphylaxis (PCA) in vivo model

[00288] Anti-Bet v 1 antibodies provided herein were tested for efficacy in blocking allergen induced mast cell degranulation in the passive cutaneous anaphylaxis (PCA) *in vivo* model. Allergen-specific antiserum is transdermally injected into a local area on the skin followed by intravenous injection of an antigen along with a dye. The allergic reaction causes capillary dilatation and increased vascular permeability at the site of sensitization, resulting in preferential accumulation of dye at this site. The dye can be extracted from the tissue and quantitated spectrophotometrically. Dye extravasation into tissue sensitized with test antiserum can then be compared to extravasation into tissue sensitized with a non-relevant antiserum.

[00289] Antisera to natural Bet v 1, Betula pendula (also known as Betula verrucosa) birch pollen extract (BPE), Betula nigra BPE, and Betula populifolia BPE were generated for use in this assay by immunizing Balb/c mice with 5µg of natural Bet v 1 protein (Indoor Biotechnologies, Catalog# NA-BV1-1 Lot 36164) or 5µg of BPE; pendula (Stallargenes Greer, Catalog# XP527D3A25 Lot #277329), nigra (Stallargenes Greer Catalog# XP79D3A25 Lot #285077) or populifolia (Stallargenes Greer Catalog# XP80D3A2.5 Lot #273622) in a solution of 1mg/ml of alum in 1X phosphate buffered saline (PBS) on day 0. One week later (day 7), sensitized mice were boosted with 5µg of natural Bet v 1 protein or 5µg of the respective BPE (pendula, nigra, or populifolia) in a solution of 1mg/mL alum in 1X PBS. Two weeks after the boost, mice were subjected to an intranasal airway challenge with 0.5µg natural Bet v 1 protein or 0.5µg of the respective birch pollen extract in 20µL of 1X PBS on days 21, 24 and 28. Mice were then sacrificed on day 31 and serum was collected. The total IgE concentration in the isolated antisera lots was determined using an OptEIA™ ELISA kit (BD Biosciences, #555248) according to the manufacturer's instructions. The final concentration of Bet v 1 antisera was diluted to 2500 ng/mL of IgE in 1X PBS and the final concentration of the birch pollen extract antisera lots were diluted to 3000 ng/mL for pendula, 1900 ng/mL for nigra and 3700 ng/mL for populifolia.

[00290] Antisera used as a negative control in this assay was generated by immunizing Balb/c mice with 5µg natural Fel d 1 protein purified from cat hair extract (Indoor Biotechnologies, Catalog# LTN-FD1-1, Lot #36099) in a solution of 1mg/mL of alum in 1X PBS. Mice were boosted with 5µg Fel d 1 protein in a solution of 1mg/mL alum in 1X PBS on days 14 and 21. One week after the final boost (day 28), mice were sacrificed and serum was collected. The total IgE concentration in the isolated antisera was determined using an

OptEIA™ ELISA kit (BD Biosciences, #555248) according to the manufacturer's instructions. The final concentration of antisera was diluted to 4800 ng/mL of IgE in PBS.

[00291] For the PCA assays, groups of Balb/c mice (n≥4 per experiment, repeated three times) were first subcutaneously injected with either an isotype control antibody or a combination of two anti-Bet v 1 antibodies at a dose of 1mg/kg (total antibody dose). Three days after antibody administration, 10μL of either 1ng Bet v 1 antisera, 25ng Betula pendula antiserum, 25ng Betula nigra antiserum, or 25ng Betula populifolia antiserum was injected into the right ear of mice in assigned groups. Left ears were administered 1ng or 25ng Fel d 1 (negative control) to match antiserum concentration of the corresponding right ear. Twenty-four hours after the local administration of allergen-specific antisera, mice were challenged by intravenous injection (100μL per mouse) with a solution of 1 μg/mL natural Bet v 1 (Catalog# NA-BV1-1, Lot 36164) or 1 μg/mL of the respective BPE (Stallargenes Greer, Catalog# XP527D3A25 Lot #277329, Catalog# XP79D3A25 Lot #285077, and Catalog# XP80D3A2.5 Lot #273622) dissolved in 1X PBS containing 0.5% (w/v) Evan's blue dye (Sigma Aldrich, #E2129). One hour after antigen challenge, mice were sacrificed, ears were excised, placed in 1 mL formamide and subsequently incubated for 3 days at 50°C to extract the Evan's blue dye. The ear tissue was then removed from the formamide, blotted to remove excess liquid and weighed. Two-hundred microliter aliquots of each formamide extract were transferred to 96 well plates in duplicate. Absorbance of the resulting supernatants was measured at 620nm. The optical density measured was converted to Evan's blue dye concentration using a standard curve and is represented as ng of Evan's blue dye per mg ear tissue. Mean values ± the standard deviation are shown in Table 1 for each group. Mean difference as compared to isotype control was calculated using Bonferroni's multiple comparisons test in GraphPad Prism.

[00292] Table 16 demonstrates efficacy of the combination of two anti-Bet v 1 antibodies, H4H16992P and H4H17082P2, indicated by a significant reduction of dye extravasation when compared to isotype control in all groups tested. As shown, the two anti-Bet v 1 monoclonal antibody combination of H4H17082P2/H4H16992P blocks mast cell degranulation in the passive cutaneous *in vivo* model against sensitization and subsequent challenge with natural Bet v 1 compared to the isotype control, demonstrating a significant reduction in dye extravasation of 88.34. Similarly, reduction of dye extravasation is also observed in H4H17082P2/H4H16992P treated groups for all three birch pollen extracts as compared to respective isotype control groups with statistically significant reductions of 62.52 for Betula pendula, 71.19 for Betula nigra, and 91.47 for Betula populifolia. The mean

difference as compared to isotype control was calculated by two-way ANOVA with Bonferroni's post test. The number of mice used per group (n) is noted within parentheses in the tables.

Table 16: Effect of anti-Bet v 1 antibodies in the passive cutaneous anaphylaxis (PCA) in-vivo model

Sensitization and Treatment	Negative control allergen (ng Evans Blue/mg tissue ±SD)	Mean Difference compared to Isotype control	Bet v 1 or BPE (ng Evans Blue/mg tissue ±SD)	Mean Difference compared to Isotype control
1ng nBet v 1 H4H17082P2+ H4H16992P (n≥14)	7.59 ± 3.03	0.7623	9.56 ± 3.53	**-88.34 (****)**
25ng Betula pendula H4H17082P2+ H4H16992P (n≥14)	7.76 ± 3.38	0.7337	15.54 ± 8.21	**-62.52 (****)**
25ng Betula nigra H4H17082P2+ H4H16992P (n≥14)	8.16 ± 4.44	1.05	23.94 ± 18.32	**-71.19 (****)**
25ng Betula populifolia H4H17082P2+ H4H16992P (n≥14)	7.11 ± 2.37	0.5416	10.09 ± 5.90	**-91.47 (****)**

1mg/kg total antibody concentration used for all antibody treatment groups
*P≤.05, ***P≤.001, ***P≤.0001
n= number of mice per group

Example 9: Cross-Competition Between Anti-Bet v 1 Monoclonal Antibodies

[00293] Binding competition within a panel of anti-Bet v 1 monoclonal antibodies was determined using a real time, label-free bio-layer interferometry assay on the Octet HTX biosensor platform (Pall ForteBio Corp.). The entire experiment was performed at 25°C in 10mM HEPES, 150mM NaCl, 3mM EDTA, and 0.05% v/v Surfactant Tween-20, 1mg/mL BSA, pH 7.4 (HBS-EBT) buffer with the plate shaking at the speed of 1000 rpm. To assess whether 2 antibodies were able to compete with one another for binding to their respective epitopes on the recombinant mutant Bet v 1 expressed with a C-terminal myc-myc-hexahistidine tag (mutant Bet v 1-MMH; SEQ ID NO: 312), around ~0.21nm of mutant Bet v 1-MMH was first captured onto anti-Penta-His antibody coated Octet biosensor tips (Fortebio

Inc, # 18-5122) by submerging the biosensor tips for 90 seconds in wells containing 5µg/mL solution of mutant Bet v 1-MMH. The antigen captured biosensor tips were then saturated with the first anti-Bet v 1 monoclonal antibody (referred to as mAb-1) by dipping into wells containing 50µg/mL solution of mAb-1 for 4 minutes. The biosensor tips were then dipped into wells containing 50µg/mL solution of second anti-Bet v 1 monoclonal antibody (referred to as mAb-2) for 3 minutes. The biosensor tips were washed in HBS-EBT buffer between every step of the experiment. The real-time binding response was monitored during the entire course of the experiment and the binding response at the end of every step was recorded. The response of mAb-2 binding to mutant Bet v 1-MMH pre-complexed with mAb-1 was compared and competitive/non-competitive behavior of different anti-Bet v 1 monoclonal antibodies was determined as shown in Table 17.

[00294] Three out of 20 anti-Bet v 1 monoclonal antibodies did not bind to mutant Bet v 1-MMH and cross-competition data was found to be inconclusive.

Table 17. Cross-competition between anti-Bet v 1 monoclonal antibodies

mAb-1	mAb-2 that competes with mAb-1
H4H17082P2	H4H16971P
H4H16971P	H4H17082P2
	H4H17027P
	H4H17028P
	H4H16946P
	H4H17038P2
H4H17027P	H4H16971P
	H4H17028P
	H4H16946P
	H4H17038P2
	H4H16950P
H4H17028P	H4H16971P
	H4H17027P
	H4H16946P
	H4H17038P2

	H4H16950P
H4H16946P	H4H16971P
	H4H17027P
	H4H17028P
	H4H17038P2
	H4H16950P
H4H17038P2	H4H16971P
	H4H17027P
	H4H17028P
	H4H16946P
	H4H16950P
	H4H16979P
H4H16950P	H4H17027P
	H4H17028P
	H4H16946P
	H4H17038P2
	H4H17015P
H4H16987P	H4H17045P2
	H4H17067P2
	H4H16967P
H4H17045P2	H4H16987P
	H4H17067P2
	H4H16967P
	H4H17015P
H4H17067P2	H4H16987P
	H4H17045P2
	H4H16967P
	H4H17015P
H4H16967P	H4H16987P
	H4H17045P2
	H4H17067P2
	H4H17015P

	H4H16992P
H4H17015P	H4H16950P
	H4H17045P2
	H4H17067P2
	H4H16967P
	H4H16979P
	H4H16991P
	H4H17033P
	H4H16992P
H4H16979P	H4H17038P2
	H4H17015P
	H4H16991P
	H4H17033P
	H4H16992P
H4H16991P	H4H17015P
	H4H16979P
	H4H17033P
	H4H16992P
H4H17033P	H4H17015P
	H4H16979P
	H4H16991P
	H4H16992P
H4H16992P	H4H16967P
	H4H17015P
	H4H16979P
	H4H16991P
	H4H17033P
	H4H16960P
	H4H17031P
H4H16960P	H4H16992P
	H4H17031P
H4H17031P	H4H16992P

	H4H16960P
H4H16943P	IC*
H4H17001P	IC*

*IC indicates that anti-Bet v 1 monoclonal antibodies did not bind to mutant Bet v 1-MMH and cross-competition data was found to be inconclusive.

Example 10. The Ability of Anti-Bet v 1 Antibody Combinations to Block Mast Cell Degranulation Induced by Bet v 1 in a Humanized Mouse PCA Model

[00295] To explore the polyclonality of the allergen-specific IgE response across human birch allergic individuals, a humanized FcεR1α mouse model was utilized to facilitate binding of human IgE to FcεR1α on the surface of mouse mast cells. Since human IgE cannot bind mouse FcεR1α, a genetically modified mouse was created where endogenous mouse FcεR1α was replaced by the corresponding human FcεR1α sequence and denoted as *FcεR1α*$^{hu/hu}$. The *FcεR1α*$^{hu/hu}$ mice were validated for use in this model by demonstrating surface expression of human FcεR1α and the ability to respond to allergen:IgE activation in the Passive Cutaneous Anaphylaxis (PCA) model in a manner comparable to wild type mice. This PCA model involves intradermal injection of allergic human sera into a local area on the skin followed by intravenous injection of relevant allergen along with a dye. The allergic reaction causes capillary dilatation and increased vascular permeability at the site of sensitization, resulting in preferential accumulation of dye at this site. The dye can be extracted from the tissue and quantitated spectrophotometrically. Dye extravasation into tissue sensitized with test antiserum is compared to extravasation into tissue sensitized with a non-allergic human sera.

Methods

[00296] To determine the effect of anti-Bet v 1 antibodies on mast cell degranulation in this model, humanized FcεR1α mice received a subcutaneous injection of isotype control antibody or anti-Bet v 1 antibody combinations on day 1. For each human donor, two independent experiments were performed, n=5 mice per group with data combined. Groups consist of no monoclonal antibody negative control, isotype negative control, REGN5713+REGN5715 dual anti-Bet v 1 antibody treatment group and REGN5713+REGN5714+REGN5715 triple anti-Bet v 1 antibody treatment group. The total or combined antibody concentration was 1mg/kg or an IgG4 isotype control antibody (anti-IL6Rα as a negative isotype control). Three days later, serum from birch allergic patients or

serum from non-birch allergic patients (negative control) was injected intradermally (ID) into the right and left ears, respectively, allowing allergen-specific IgE to bind FcεRI on mast cells. To ensure that the same amount of allergen specific IgE from each donor was used in the experiment, each antiserum injection was normalized to a Bet v 1-specific IgE ImmunoCAP® of 10 KU_a/L.

[00297] Twenty–four hours after local administration of allergen-specific antibodies, mice were challenged by IV injection of 1μg Bet v 1 diluted in PBS containing 0.5% Evan's blue dye. One hour after allergen challenge, mice were sacrificed. Evan's blue dye was extracted from ear tissue and quantitated spectrophotometrically using a standard curve. (See Figure 6 for diagram of protocol used.) The reduction in Evan's blue dye extravasation was calculated on average by subtracting the concentration of Evan's blue dye (normalized by ear tissue weight) for the antibody-treated group's birch allergic serum administered ear, B(mAb,i), from the group treated with isotype control antibody, B(isotype,avg). This number was then divided by the difference between B(isotype,avg) and the dye concentration for antibody-treated group's non-allergic serum administered ear [N(mAb,i)] and multiplied by 100 to give the overall average percent reduction in dye extravasation (% Reduction). The equation is shown below:

% Reduction (average) = 100*[B(isotype,avg) – B(mAb,i)]/[B(isotype,avg) – N(mAb,i)]

[00298] An increase in the percent reduction in dye leakage in the anti-Bet v1 antibody treated group compared to the negative isotype control group is a measure of effectiveness of the Bet v 1 antibody or antibody combinations in blocking mast cell degranulation.

Results

[00299] In this model, the combined use of anti-Bet v 1 antibodies designated H4H16992P (also referred to as REGN5713), H4H17038P2 (also referred to as REGN5714) and H4H17082P2 (also referred to as REGN5715) demonstrated maximal blocking of the IgE mediated response when using IgE containing sera from 3/3 birch allergic donors (See Figure 7). Using sera from birch allergic donor 25609, H4H16992P, H4H17038P2 and H4H17082P2 when combined exhibited 95% blockade of mast cell degranulation compared to isotype control (mean difference -42.04 +/-6.9 ($p<0.0001$)), and the combined use of H4H16992P and H4H17082P2 exhibited 93% blockade of mast cell degranulation compared to isotype control (mean difference -41.74 +/-3.7 ($p<0.0001$)). Using sera from birch allergic donor 23658, H4H16992P, H4H17038P2 and H4H17082P2, when combined exhibited 90% blockade of mast cell degranulation compared to isotype control (mean difference-53.67 +/-

7.1 ($p<0.0001$)) and H4H16992P combined with H4H17082P2 exhibited 74% blockade of mast cell degranulation compared to isotype control (mean difference -44.58 +/-11.4 ($p<0.0001$)). Finally, using sera from birch allergic donor 25414, H4H16992P, H4H17038P2 and H4H17082P2, when combined exhibited 92% blockade of mast cell degranulation compared to isotype control (mean difference -39.72 +/-7.5 ($p<0.0001$)) and H4H16992P combined with H4H17082P2 exhibited 80% blockade of mast cell degranulation compared to isotype control (mean difference -34.27 +/-7.8 ($p<0.0001$)).

Example 11. The Ability of Anti-Bet v 1 Antibody Combinations to Block Basophil Activation in the Phospho-Erk Phosphoflow Assay

[00300] The human IgE response was explored by testing the effect of various combinations of the anti- Bet v 1 antibodies H4H16992P (also referred to as REGN5713), H4H17038P2 (also referred to as REGN5714) and H4H17082P2 (also referred to as REGN5715) on inhibiting basophil activation using samples from 8 birch allergic individuals. More specifically, to assess FcεR engagement and activation, basophils were tested in a functional phosphoflow based assay that measures phosphorylation of the kinase ERK, a proximal readout of basophil activation and degranulation (Liu, Y. et al. (2007), *J Exp Med* 204, 93-103.

Methods

[00301] Blood was drawn from birch allergic patients (n=8) and PBMCs isolated by density centrifugation on a Ficoll layer, washed, resuspended and plated as single points in a 96-well format. In parallel, a 2X stimulation plate was prepared that included a dose response of purified Bet v 1 as well as dose responses of anti-Bet v 1 antibodies and antibody combinations (2.56pM-200nM) mixed with a constant dose (final concentration 100pM) of purified natural Bet v 1. The cells were stimulated and subsequently stained with an antibody cocktail containing pErk-Alexa 488, CD123-BUV395 and HLA-DR-APC antibodies. Following staining, data was acquired using an LSR-Fortessa instrument and analyzed by calculating the MFI of phosphorylated Erk staining within the basophil gate. Percent Max Inhibition was calculated as: 100 – ((100 X Maximum Antibody Response)/Isotype Response). Maximum antibody response was the average Median Fluorescence Intensity (MFI) of phosphorylated Erk in the top three doses of antibody in the dose response curve (plateau of the curve) minus the baseline MFI (average of replicate unstimulated samples), and isotype response is the average of all the MFI values in the dose response of a Regeneron produced isotype control antibody (REGN1945 anti-Fel d 1 $IgG4^{P}$) minus the baseline MFI.

Results

[00302] Basophils from all 8-birch pollen-allergic individuals responded to Bet v 1 stimulation with varying intensities. See Figure 8. H4H16992P, H4H17038P2 and H4H17082P2 inhibited at least 70% of basophil activation in 8/8 donors, while the combination of H4H16992P with H4H17082P2 achieved the same magnitude of inhibition in 6/8 donors. Notably, the individual antibodies when tested separately showed a high degree of variability in the ability to impact allergen binding to IgE. H4H16992P achieved ≥70% blockade in 3/8 donors and H4H17082P2 achieved 70% blockade of basophil activation in 4/8 donors. H4H17038P2 demonstrated 70% blocking in only 1/8 donors tested.

Example 12: Determination of Simultaneous Binding of Three Anti-Bet v 1 Monoclonal Antibodies to Natural Bet v 1

[00303] This experiment was performed to ensure that the binding epitopes of three select Bet v 1 monoclonal antibodies were unique and that, irrespective of the order of monoclonal antibody binding, no steric hindrance was exhibited upon simultaneous binding of the three antibodies. Order dependent competition between the three Bet v 1 monoclonal antibodies was also assessed.

[00304] Simultaneous binding of three anti-Bet v 1 monoclonal antibodies to the same Bet v 1 was determined using a real time, label-free surface plasmon resonance based Biacore 3000 biosensor platform (GE Healthcare.). The entire experiment was performed at 25°C in running buffer containing 10mM HEPES, 150mM NaCl, 3mM EDTA, and 0.05% v/v Surfactant Tween-20, pH7.4 (HBS-ET). The antibodies were immobilized on different surfaces of CM5 sensor using EDC/NHS chemistry to achieve immobilization levels of 5000 – 13,000 RU. REGN1945 (Fel d 1 monoclonal antibody) was also immobilized as the negative control. Natural Bet v 1 (nBet v 1), 10nM or 20nM, was injected over different Bet v 1 monoclonal antibody immobilized sensor surfaces for 10-12 seconds followed by sequential injection of different Bet v 1 monoclonal antibodies for 6 minutes at 15µL/min.

[00305] The binding of different Bet v 1 monoclonal antibodies to nBet v 1 bound to a monoclonal antibody immobilized sensor surface was measured using Scrubber 2.0c. The results are shown in Table 18. A binding signal of less than 1 RU (Resonance Unit) indicates that no binding was observed when the Bet v 1 monoclonal antibody was injected, while a higher binding signal (greater than 2 RU) represents no competition. All three Bet v 1 monoclonal antibodies included in this example were able to simultaneously bind to nBet v 1 and binding response was not affected by the order in which the antibodies were added.

Table 18: Anti-Bet v 1 Antibody Simultaneous Binding Competition

		Sequential Binding of 3 Bet v 1 monoclonal antibodies					
Bet v 1 monoclonal antibody Immobilized on Surface	**nBet v 1 Binding (RU)**	**mAb-1**	**mAb-1 Binding (RU)**	**mAb-2**	**mAb-2 Binding (RU)**	**mAb-3**	**mAb-3 Binding (RU)**
REGN5713	10	REGN5713	0	REGN5714	59	REGN5715	44
	11		0	REGN5715	48	REGN5714	53
	10	REGN5714	59	REGN5713	-3	REGN5715	43
	10		60	REGN5715	43	REGN5713	-6
	10	REGN5715	46	REGN5713	-4	REGN5714	54
	10		46	REGN5714	54	REGN5713	-5
REGN5714	14	REGN5713	67	REGN5714	-4	REGN5715	40
	14		63	REGN5715	38	REGN5714	-5
	13	REGN5714	1	REGN5713	48	REGN5715	30
	13		1	REGN5715	35	REGN5713	42
	12	REGN5715	42	REGN5713	47	REGN5714	-3
	12		40	REGN5714	-2	REGN5713	44
REGN5715	14	REGN5713	62	REGN5714	69	REGN5715	-5
	14		60	REGN5715	-4	REGN5714	67
	13	REGN5714	73	REGN5713	56	REGN5715	-5
	13		73	REGN5715	-3	REGN5713	54
	12	REGN5715	-1	REGN5713	51	REGN5714	65
	12		0	REGN5714	69	REGN5713	47

Data represents average of at least 3 independent injections of Bet v 1 monoclonal antibodies over the complex of nBet v 1 and immobilized Bet v 1 monoclonal antibody

Summary

[00306] Regardless of the order of antibody binding to Bet v 1, there was no competition impeding the simultaneous binding of all three antibodies, suggesting that REGN5713, REGN5714, and REGN5715 bind to non-overlapping, distinct epitopes.

[00307] The term "comprising" as used in this specification and claims means "consisting at least in part of". When interpreting statements in this specification and claims which include the term "comprising", other features besides the features prefaced by this term

in each statement can also be present. Related terms such as "comprise" and "comprises" are to be interpreted in similar manner.

[00308] In this specification where reference has been made to patent specifications, other external documents, or other sources of information, this is generally for the purpose of providing a context for discussing the features of the invention. Unless specifically stated otherwise, reference to such external documents is not to be construed as an admission that such documents, or such sources of information, in any jurisdiction, are prior art, or form part of the common general knowledge in the art.

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CLAIMS

The claims defining the invention are as follows:

1. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to natural Bet v 1 or birch pollen extract (BPE), wherein the antibody or fragment thereof comprises:
(a) a heavy chain complementarity determining region (HCDR)1 comprising the amino acid sequence of SEQ ID NO: 292; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 294; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 296; a light chain complementarity determining region (LCDR)1 comprising the amino acid sequence of SEQ ID NO: 300; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 302; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 304; or
(b) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 148; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 150; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 152; an LCDR1 comprising the amino acid sequence of SEQ ID NO: 156; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 158; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 160; or
(c) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 100; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 102; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 104; an LCDR1 comprising the amino acid sequence of SEQ ID NO: 108; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 110; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 112; or
(d) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 116; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 118; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 120; an LCDR1 comprising the amino acid sequence of SEQ ID NO: 124; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 126; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 128; or
(e) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8; an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16; or

(f) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 20; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 22; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 24; an LCDR1 comprising the amino acid sequence of SEQ ID NO: 28; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 30; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 32; or

(g) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 36; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 38; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 40; an LCDR1 comprising the amino acid sequence of SEQ ID NO: 44; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 46; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 48; or

(h) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 52; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 54; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 56; an LCDR1 comprising the amino acid sequence of SEQ ID NO: 60; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 62; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 64; or

(i) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 68; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 70; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 72; an LCDR1 comprising the amino acid sequence of SEQ ID NO: 76; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 78; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 80; or

(j) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 84; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 86; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 88; an LCDR1 comprising the amino acid sequence of SEQ ID NO: 92; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 94; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 96; or

(k) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 132; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 134; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 136; an LCDR1 comprising the amino acid sequence of SEQ ID NO: 140; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 142; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 144; or

(l) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 164; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 166; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 168; an LCDR1 comprising the amino acid sequence of SEQ

ID NO: 172; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 174; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 176; or

(m) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 180; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 182; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 184; an LCDR1 comprising the amino acid sequence of SEQ ID NO: 188; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 190; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 192; or

(n) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 196; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 198; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 200; an LCDR1 comprising the amino acid sequence of SEQ ID NO: 204; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 206; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 208; or

(o) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 212; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 214; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 216; an LCDR1 comprising the amino acid sequence of SEQ ID NO: 220; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 222; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 224; or

(p) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 228; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 230; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 232; an LCDR1 comprising the amino acid sequence of SEQ ID NO: 236; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 238; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 240; or

(q) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 244; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 246; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 248; an LCDR1 comprising the amino acid sequence of SEQ ID NO: 252; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 254; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 256; or

(r) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 260; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 262; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 264; an LCDR1 comprising the amino acid sequence of SEQ ID NO: 268; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 270; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 272; or

(s) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 276; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 278; an HCDR3 comprising the amino

acid sequence of SEQ ID NO: 280; an LCDR1 comprising the amino acid sequence of SEQ ID NO: 268; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 270; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 272; or
(t) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 284; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 286; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 288; an LCDR1 comprising the amino acid sequence of SEQ ID NO: 268; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 270; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 272.

2. The antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof is a fully human monoclonal antibody.

3. The antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable/light chain variable region (HCVR/LCVR) amino acid sequence pair selected from the group consisting of SEQ ID NOs: 146/154, 290/298, 98/106, 114/122, 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 130/138, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/266, and 282/266.

4. The antibody or antigen-binding fragment thereof of claim 3, comprising an HCVR comprising the amino acid sequence of SEQ ID NO: 146 and an LCVR comprising the amino acid sequence of SEQ ID NO:154.

5. The antibody or antigen-binding fragment thereof of claim 1, wherein the BPE is from Betula pendula, Betula nigra, or Betula populifolia.

6. The antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof cross-reacts with one or more allergens selected from the group consisting of Aln g1, Cor a1, Car b1, Que a1, Api g2, Api g1, Dau c1, Mal d1, Ost c1, Fag s1, and Cas s1.

7. The antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof binds to Bet v 1 with a KD equal to or less than 10-8 M as measured by surface plasmon resonance.

8. A pharmaceutical composition comprising a therapeutically effective amount of an antibody or antigen-binding fragment thereof of claim 1 and a pharmaceutically acceptable excipient.

9. The isolated monoclonal antibody or antigen-binding fragment thereof of claim 1, comprising:

an HCDR1 comprising the amino acid sequence of SEQ ID NO: 148; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 150; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 152; an LCDR1 comprising the amino acid sequence of SEQ ID NO: 156; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 158; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 160.

10. The isolated monoclonal antibody or antigen-binding fragment thereof of claim 1, comprising:

an HCDR1 comprising the amino acid sequence of SEQ ID NO: 292; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 294; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 296; an LCDR1 comprising the amino acid sequence of SEQ ID NO: 300; an LCDR2 comprising the amino acid sequence of SEQ ID NO: 302; and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 304.

11. The isolated monoclonal antibody or antigen-binding fragment thereof of claim 1, comprising:

an HCDR1 comprising the amino acid sequence of SEQ ID NO: 100; an HCDR2 comprising the amino acid sequence of SEQ ID NO: 102; an HCDR3 comprising the amino acid sequence of SEQ ID NO: 104; an LCDR1 comprising the amino acid sequence of SEQ ID NO: 108, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 110, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 112.

12. A pharmaceutical composition comprising a therapeutically effective amount of an antibody or antigen-binding fragment thereof of claim 9 and a pharmaceutically acceptable excipient.

13. A pharmaceutical composition comprising a therapeutically effective amount of an antibody or antigen-binding fragment thereof of claim 10 and a pharmaceutically acceptable excipient.

14. A pharmaceutical composition comprising a therapeutically effective amount of an antibody or antigen-binding fragment thereof of claim 11 and a pharmaceutically acceptable excipient.

15. The antibody or antigen-binding fragment thereof of claim 3, comprising an HCVR comprising the amino acid sequence of SEQ ID NO: 290 and an LCVR comprising the amino acid sequence of SEQ ID NO: 298.

16. The antibody or antigen-binding fragment thereof of claim 3, comprising an HCVR comprising the amino acid sequence of SEQ ID NO: 98 and an LCVR comprising the amino acid sequence of SEQ ID NO: 106.

17. The antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof binds to a Bet v 1 amino acid sequence fragment selected from the group consisting of SEQ ID NOs: 307, 308, 309, 310, and 311.

18. The antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof inhibits natural Bet v 1, Betula pendula BPE, Betula nigra BPE, or Betula populifolia BPE binding to allergen specific IgE.

19. A method of preventing or reducing mast cell degranulation or blocking basophil activation associated with natural Bet v 1, Betula pendula BPE, Betula nigra BPE, or Betula populifolia BPE sensitization, the method comprising administering an antibody or antigen-binding fragment thereof of any one of claims 1 through 11 or 15 through 18 or a pharmaceutical composition of any one of claims 12 through 14 to a patient in need thereof.

20. Use of an antibody or an antigen-binding fragment thereof of any one of claims 1 through 11 or 15 through 18, or a pharmaceutical composition of any one of claims 12 through 14, in the manufacture of a medicament for use in preventing or reducing mast cell

degranulation or blocking basophil activation associated with natural Bet v 1, Betula pendula BPE, Betula nigra BPE, or Betula populifolia BPE sensitization.

21. A method for treating a patient who demonstrates a sensitivity to, or an allergic reaction against, a Fagales protein, a Fagales allergen, birch pollen or an extract thereof, or Bet v 1 protein, or for treating at least one symptom or complication associated with a sensitivity to, or allergic reaction against a Fagales protein, a Fagales allergen, birch pollen or an extract thereof, or Bet v 1 protein, the method comprising administering an effective amount of one or more isolated human monoclonal antibodies or antigen-binding fragments thereof of any one of claims 1 through 11 or 15 through 18, or a pharmaceutical composition of any one of claims 12 through 14, to a patient in need thereof, wherein the sensitivity to, or an allergic reaction against, a Fagales protein, a Fagales related allergen, birch pollen or an extract thereof, or Bet v 1 protein is either prevented, or lessened in severity and/or duration, or at least one symptom or complication associated with the sensitivity to, or allergic reaction against, a Fagales protein, a Fagales related allergen, birch pollen or an extract thereof, or Bet v 1 protein is prevented, or ameliorated, or that the frequency and/or duration of, or the severity of the sensitivity to or allergic reaction against, a Fagales protein, a Fagales related allergen, birch pollen or an extract thereof, or Bet v 1 protein is reduced following administration of one or more of the isolated human monoclonal antibodies or fragments thereof that bind Bet v 1, or following administration of a composition comprising any one or more of the foregoing antibodies.

22. Use of an antibody or antigen-binding fragment thereof of any one of claims 1 through 11 or 15 through 18, or a pharmaceutical composition of any one of claims 12 through 14 in the manufacture of a medicament for use in treating a patient who demonstrates a sensitivity to, or an allergic reaction against, a Fagales protein, a Fagales allergen, birch pollen or an extract thereof, or Bet v 1 protein, or for treating at least one symptom or complication associated with a sensitivity to, or allergic reaction against a Fagales protein, a Fagales allergen, birch pollen or an extract thereof, or Bet v 1 protein.

23. The method of claim 21 or the use of claim 22, wherein the birch pollen extract is selected from the group consisting of natural Bet v 1, Betula pendula BPE, Betula nigra BPE, and Betula populifolia BPE.

24. The method of claim 21 or the use of claim 22, wherein the Fagales allergen is selected from the group consisting of Bet v 1, Aln g1, Cor a1, Car b1, and Que a1.

25. A method for enhancing the efficacy and/or safety of an allergen-specific immunotherapy (SIT) regimen, the method comprising administering an effective amount of one or more antibodies or antigen-binding fragments thereof of any one of claims 1 through 11 or 15 through 18, or a pharmaceutical composition of any one of claims 12 through 14, to a patient in need thereof just prior to or concurrent with the SIT regimen, wherein the severity of an allergic reaction to the SIT regimen is mitigated.

26. Use of an antibody or antigen-binding fragment thereof of any one of claims 1 through 11 or 15 through 18, or a pharmaceutical composition of either claims 13 or 14, in the manufacture of a medicament for use in enhancing the efficacy and/or safety of an allergen-specific immunotherapy (SIT) regimen.

27. The method of claim 25 or the use of claim 26, wherein the SIT regimen comprises an up-dosing phase followed by a maintenance phase.

28. The method of claim 25 or the use of claim 26, wherein the SIT regimen is a rush SIT regimen.

29. A nucleic acid molecule encoding the human monoclonal antibody or antigen-binding fragment thereof of any one of claims 1 through 11 or 15 through 18.

30. An expression vector comprising the nucleic acid molecule of claim 29.

31. A host cell containing the expression vector of claim 30.

Bet v 1 peptides with significant protection upon binding to H4H16992P

Bet v 1	1 minute Deuteration			5 minutes Deuteration		
	Bet v 1	Bet v 1 + H4H16992P		Bet v 1	Bet v 1 + H4H16992P	
	Centroid MH^+	Centroid MH^+	Δ	Centroid MH^+	Centroid MH^+	Δ
23-38	1748.25	1747.47	**-0.78**	1749.37	1747.81	**-1.56**
23-41	2035.88	2035.14	**-0.74**	2037.97	2035.48	**-2.49**
23-43	2265.54	2264.25	**-1.29**	2267.30	2264.60	**-2.70**
26-43	1890.50	1889.99	**-1.80**	1891.61	1890.02	**-1.58**
29-43	1603.03	1602.35	**-0.67**	1603.78	1602.49	**-1.29**

Bet v 1	10 minutes Deuteration			20 minutes Deuteration		
	Bet v 1	Bet v 1 + H4H16992P		Bet v 1	Bet v 1 + H4H16992P	
	Centroid MH^+	Centroid MH^+	Δ	Centroid MH^+	Centroid MH^+	Δ
23-38	1750.00	1748.05	**-1.95**	1750.83	1748.28	**-2.55**
23-41	2038.68	2035.86	**-2.82**	2039.74	2035.62	**-4.12**
23-43	2267.93	2264.97	**-2.97**	2268.94	2265.22	**-3.72**
26-43	1892.36	1890.15	**-2.22**	1893.15	1890.20	**-2.95**
29-43	1604.51	1602.69	**-1.82**	1605.34	1602.76	**-2.59**

Figure 1

Bet v 1 peptides with significant protection upon binding to H4H17082P

Bet v 1	1 minute Deuteration			5 minutes Deuteration		
	Bet v 1	Bet v 1 + H4H17082P2		Bet v 1	Bet v 1 + H4H17082P2	
Peptide range	Centroid MH^+	Centroid MH^+	Δ	Centroid MH^+	Centroid MH^+	Δ
44-56	1289.33	1286.44	**-2.89**	1289.83	1286.68	**-3.16**
44-70	2948.26	2945.90	**-2.36**	2949.94	2946.68	**-3.26**
45-56	1174.64	1172.13	**-2.50**	1175.00	1172.18	**-2.83**
57-66	1172.15	1172.31	0.16	1172.33	1172.62	0.29
57-70	1678.31	1678.21	-0.10	1678.93	1678.90	-0.03

Bet v 1	10 minutes Deuteration			20 minutes Deuteration		
	Bet v 1	Bet v 1 + H4H17082P2		Bet v 1	Bet v 1 + H4H17082P2	
Peptide range	Centroid MH^+	Centroid MH^+	Δ	Centroid MH^+	Centroid MH^+	Δ
44-56	1290.49	1286.72	**-3.77**	1290.74	1286.91	**-3.83**
44-70	2950.45	2947.01	**-3.45**	2951.12	2947.05	**-4.14**
45-56	1175.04	1172.36	**-2.69**	1175.43	1172.49	**-2.94**
57-66	1172.48	1172.46	-0.02	1172.49	1172.61	0.12
57-70	1678.94	1678.82	-0.12	1679.17	1678.89	-0.28

Figure 2

Bet v 1 peptides with significant protection upon binding to H4H17038P2

Bet v 1	1 minute Deuteration			5 minutes Deuteration		
	Bet v 1	Bet v 1 + H4H17038P2		Bet v 1	Bet v 1 + H4H17038P2	
Peptide range	Centroid MH^+	Centroid MH^+	Δ	Centroid MH^+	Centroid MH^+	Δ
2-19	1974.52	1972.83	**-1.68**	1975.52	1973.95	**-1.57**
5-10	758.44	758.01	**-0.43**	758.46	758.14	**-0.31**
5-19	1670.08	1669.3	**-0.77**	1670.94	1670.04	**-0.9**
8-19	1262.02	1261.68	**-0.34**	1262.96	1262.49	**-0.46**
11-19	929.74	929.46	**-0.28**	930.65	930.36	**-0.29**

Bet v 1	10 minutes Deuteration			20 minutes Deuteration		
	Bet v 1	Bet v 1 + H4H17038P2		Bet v 1	Bet v 1 + H4H17038P2	
Peptide range	Centroid MH^+	Centroid MH^+	Δ	Centroid MH^+	Centroid MH^+	Δ
2-19	1976.06	1974.38	**-1.68**	1976.36	1974.98	**-1.39**
5-10	758.48	758.18	**-0.31**	758.55	758.18	**-0.36**
5-19	1671.51	1670.47	**-1.04**	1671.91	1670.92	**-0.98**
8-19	1263.31	1262.9	**-0.41**	1263.57	1263.28	**-0.29**
11-19	931.1	930.7	**-0.4**	931.41	931.11	**-0.31**

Figure 3

Bet v 1 peptides with significant protection upon binding to H4H16987P

Bet v 1	1 minute Deuteration			5 minutes Deuteration		
	Bet v 1	Bet v 1 + H4H16987P		Bet v 1	Bet v 1 + H4H16987P	
Peptide range	Centroid MH^+	Centroid MH^+	Δ	Centroid MH^+	Centroid MH^+	Δ
57-66	1172.27	1169.98	**-2.38**	1172.64	1170.04	**-2.61**
57-70	1678.61	1675.67	**-2.94**	1679.17	1676.05	**-3.13**
81-96	1731.22	1730.33	**-0.89**	1731.66	1730.77	**-0.89**
85-96	1162.24	1161.44	**-0.79**	1162.25	1161.74	**-0.51**
89-96	732.56	732.41	-0.19	732.57	732.52	-0.08

Bet v 1	10 minutes Deuteration			20 minutes Deuteration		
	Bet v 1	Bet v 1 + H4H16987P		Bet v 1	Bet v 1 + H4H16987P	
Peptide range	Centroid MH^+	Centroid MH^+	Δ	Centroid MH^+	Centroid MH^+	Δ
57-66	1172.74	1170.28	**-2.46**	1172.74	1170.46	**-2.28**
57-70	1679.38	1676.22	**-3.16**	1679.44	1676.44	**-3**
81-96	1731.67	1730.95	**-0.72**	1731.8	1731.27	**-0.53**
85-96	1162.27	1161.92	**-0.34**	1162.31	1162.06	**-0.26**
89-96	732.58	732.54	-0.08	732.62	732.53	-0.13

Figure 4

Bet v 1 peptides with significant protection upon binding to 4 antibody combo of H4H16992P, H4H17082P, H4H17038P2 and H4H16987P

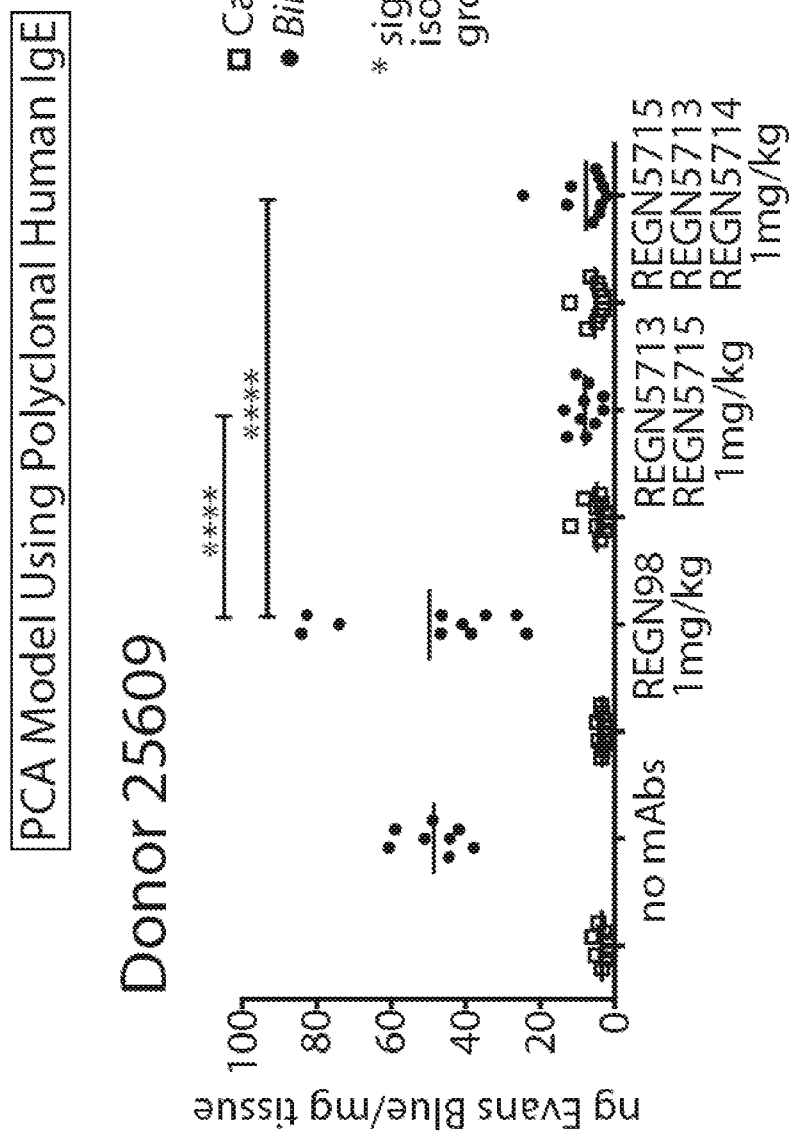
Bet v 1	1 minute Deuteration			5 minutes Deuteration		
	Bet v 1	Bet v 1 + combo		Bet v 1	Bet v1 + combo	
Peptide range	Centroid MH^+	Centroid MH^+	Δ	Centroid MH^+	Centroid MH^+	Δ
2-19	1974.69	1973.29	**-1.41**	1975.83	1973.96	**-1.89**
5-19	1670.16	1670.00	**-0.41**	1671.12	1670.00	**-1.14**
23-41	2265.84	2264.15	**-1.75**	2267.69	2264.35	**-3.39**
23-43	1228.61	1227.58	**-1.04**	1229.22	1227.62	**-1.62**
44-70	2948.40	2942.57	**-5.75**	2950.06	2943.03	**-6.94**
57-66	1171.88	1169.99	**-1.44**	1172.10	1169.99	**-1.70**
81-96	1731.58	1729.88	**-1.72**	1731.64	1729.99	**-1.67**
84-96	1325.51	1324.33	**-1.24**	1325.43	1324.67	**-1.67**

Bet v 1	10 minutes Deuteration			20 minutes Deuteration		
	Bet v 1	Bet v 1 + combo		Bet v 1	Bet v 1 + combo	
Peptide range	Centroid MH^+	Centroid MH^+	Δ	Centroid MH^+	Centroid MH^+	Δ
2-19	1976.61	1974.04	**-2.59**	1976.99	1974.04	**-3**
5-19	1671.77	1670.06	**-1.74**	1672.03	1670.12	**-1.96**
23-41	2268.43	2264.50	**-3.98**	2269.66	2264.72	**-4.99**
23-43	1230.15	1227.64	**-2.52**	1230.88	1227.71	**-3.24**
44-70	2950.52	2943.40	**-7.03**	2951.79	2943.42	**-8.28**
57-66	1172.18	1170.22	**-1.56**	1172.32	1170.09	**-1.85**
81-96	1731.76	1730.22	**-1.57**	1732.01	1730.61	**-1.49**
84-96	1325.53	1324.72	**-1.57**	1325.82	1324.98	**-1.5**

Figure 5

10uL ID non birch allergic donor antiserum (negative control)
10uL ID birch allergic donor antiserum
Control antiserum sensitized ear
Birch allergic donor antiserum sensitized ear
D1
D4
D5
SC injection of antibody or antibody cocktail
Passive administration of allergen specific IgE antiserum to each ear
Systemic challenge via IV Bet v 1 + 0.5% Evans Blue Dye

Figure 6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Cat allergic sera
Birch allergic sera
* significance to isotype control group only shown
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40
20
0
no mAbs
REGN98 1mg/kg
REGN5713 REGN5715 1mg/kg
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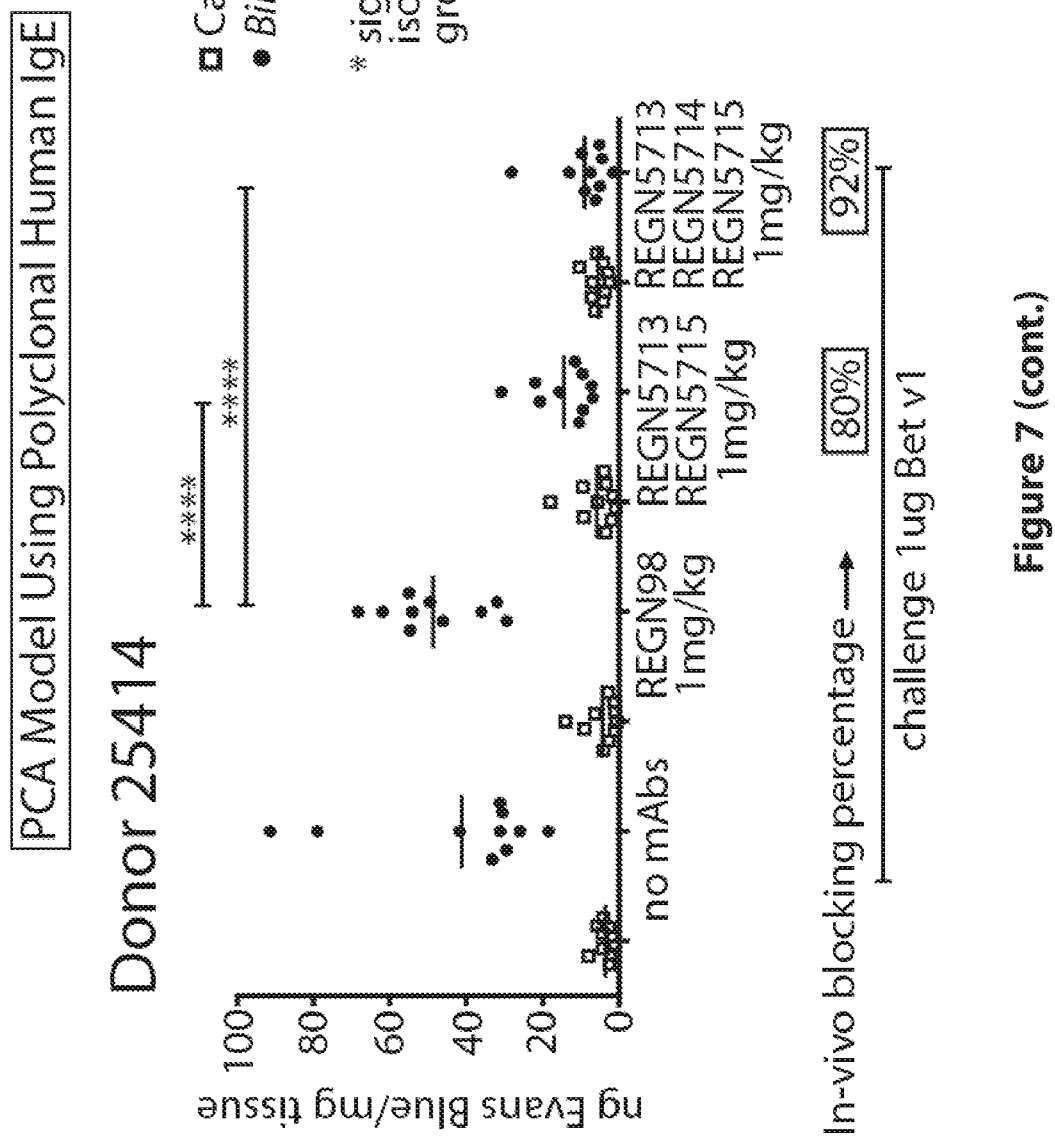
REGN5714 1mg/kg
In-vivo blocking percentage
93%
95%
challenge 1ug Bet v1

Figure 7



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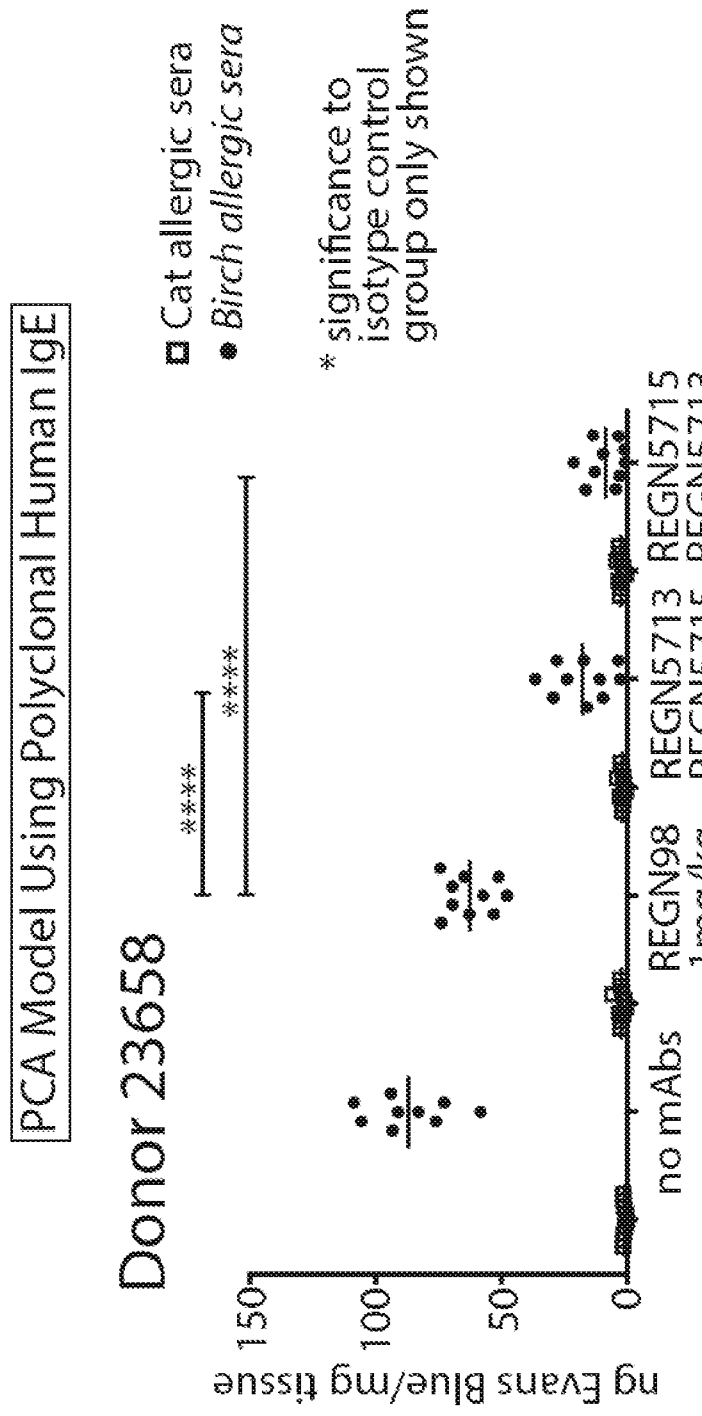

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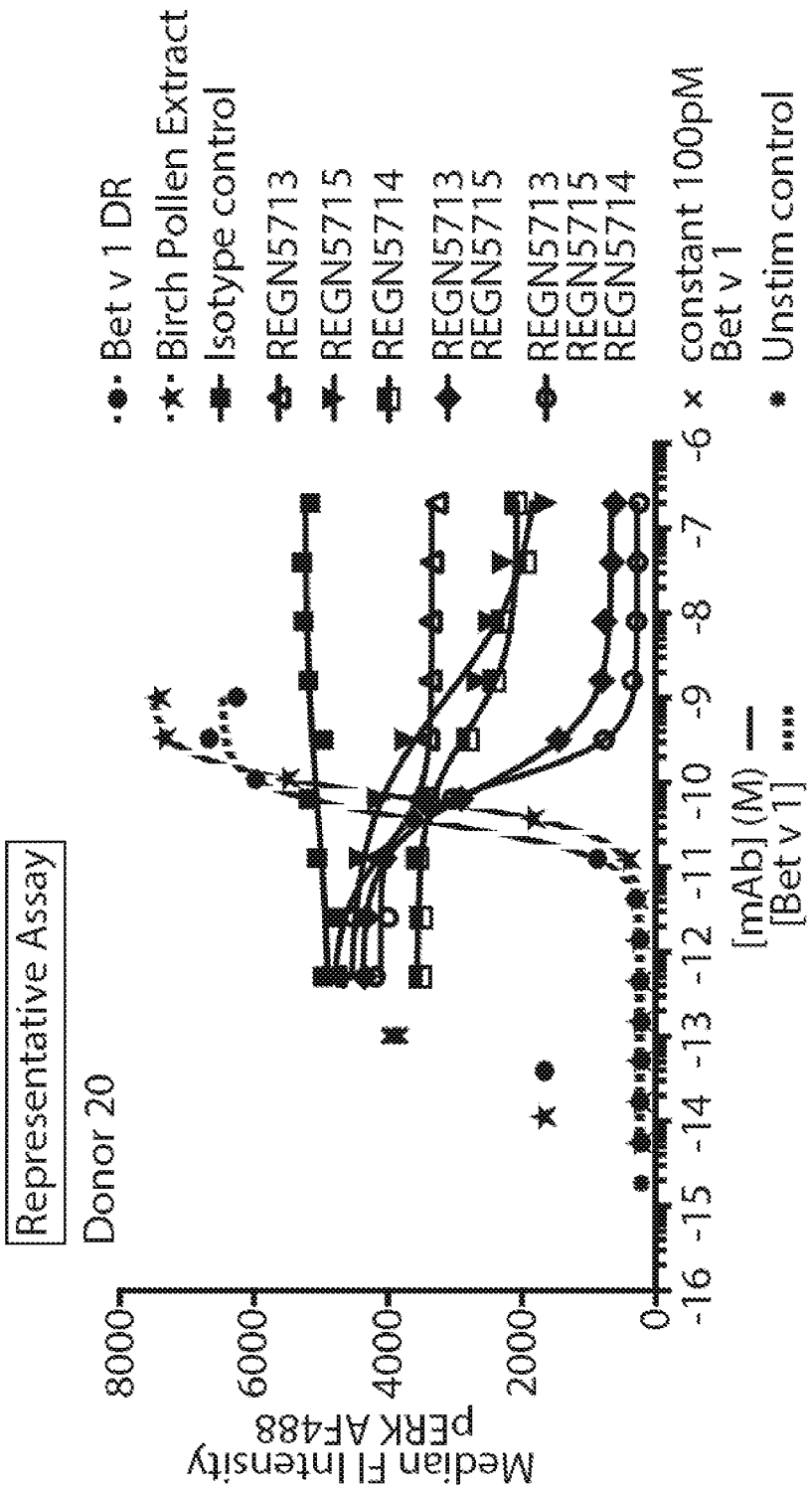
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Bet v 1 DR
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Figure 8

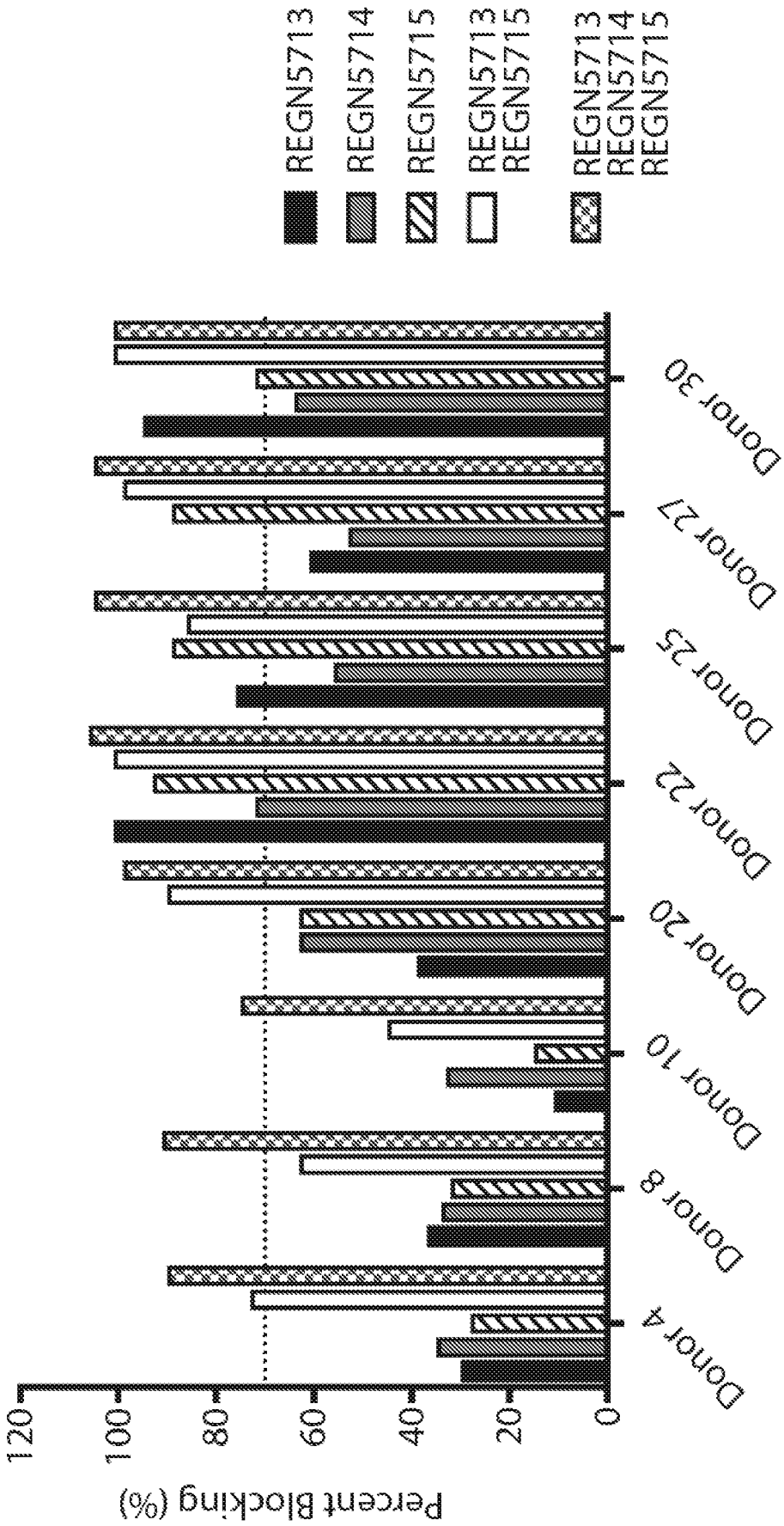

Figure 8 (cont.)

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Orengo, Jamie M.
Murphy, Andrew J.
Badithe, Ashok T.
Kamat, Vishal
Liu, Yashu

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<210> 38
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<400> 38

Ile Ser Ala Tyr Asn Gly Asn Thr
1 5

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<210> 40
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<400> 40

Ala Arg Arg Ser Ser Met Leu His Phe Gln His
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tggttccagc agaagccagg acagcctcct aaacttctca tttactgggc atctacccgg 180

gaatccgggg tccctgaccg attcagtggc agcgggtctg ggacagattt cactctcacc 240

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ccgtacactt ttggccaggg gaccaagctg gagatcaaa 339

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<400> 42

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln His Val Leu Tyr Asp
20 25 30

Ser Ser Asn Glu Asn Tyr Leu Ala Trp Phe Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
85 90 95

Tyr Ser Ser Ala Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
100 105 110

Lys

<210> 43
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<212> DNA
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<210> 44
<211> 12
<212> PRT
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<220>
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<400> 44

Gln His Val Leu Tyr Asp Ser Ser Asn Glu Asn Tyr
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<211> 9
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<220>
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<400> 45
tgggcatct 9

<210> 46
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<400> 46

Trp Ala Ser
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<210> 47
<211> 27
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<400> 47
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<210> 48
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<400> 48

Gln Gln Tyr Ser Ser Ala Pro Tyr Thr
1 5

<210> 49
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<220>
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cagcccccag ggaaggggct ggagtggatt ggtagtatct attatagcgg gatcacctac 180

tacaacccgt ccctcaagag tcgagtcacc atatccgcgg acacgtctaa ggaccagttc 240

tccctgaagc tgaggtctgt gaccgccgcg gacacggctg tgtattactg tgcgaaattg 300

gagtggctgc gcttggactt ctggggccag ggaaccacgg tcaccgtctc ctca 354

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<400> 50

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1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Ser
20 25 30

Asn Tyr Trp Trp Gly Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu
35 40 45

Trp Ile Gly Ser Ile Tyr Tyr Ser Gly Ile Thr Tyr Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Val Thr Ile Ser Ala Asp Thr Ser Lys Asp Gln Phe
65 70 75 80

Ser Leu Lys Leu Arg Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Ala Lys Leu Glu Trp Leu Arg Leu Asp Phe Trp Gly Gln Gly Thr

100 105 110

Thr Val Thr Val Ser Ser
115

<210> 51
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
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<400> 51
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<210> 52
<211> 10
<212> PRT
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<220>
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<400> 52

Gly Gly Ser Ile Ser Ser Ser Asn Tyr Trp
1 5 10

<210> 53
<211> 21
<212> DNA
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<220>
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<400> 53
atctattata gcgggatcac c 21

<210> 54
<211> 7
<212> PRT
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<220>
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<400> 54

Ile Tyr Tyr Ser Gly Ile Thr
1 5

<210> 55
<211> 30
<212> DNA
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<220>
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<400> 55
gcgaaattgg agtggctgcg cttggacttc 30

<210> 56
<211> 10
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<400> 56

Ala Lys Leu Glu Trp Leu Arg Leu Asp Phe
1 5 10

<210> 57
<211> 321
<212> DNA
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<220>
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<400> 57
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gggaaagtcc ccaagctcct gatctatgct gcatccagtt tacaaagtgg ggtcccatta 180

aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240

gaagattttg caacttacta ttgtcaacag gctaaaagtt tccctctcac cttcggccaa 300

gggacacgac tggagattaa a 321

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<211> 107
<212> PRT
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<220>
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<400> 58

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30

Leu Val Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Leu Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Lys Ser Phe Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 59
<211> 18
<212> DNA
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<220>
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<400> 59
cagggtatta gtagctgg 18

<210> 60
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
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<400> 60

Gln Gly Ile Ser Ser Trp
1 5

<210> 61
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
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<400> 61
gctgcatcc 9

<210> 62
<211> 3
<212> PRT
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<220>
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<400> 62

Ala Ala Ser
1

<210> 63
<211> 27
<212> DNA
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<400> 63
caacaggcta aaagtttccc tctcacc 27

<210> 64
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<212> PRT
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Gln Gln Ala Lys Ser Phe Pro Leu Thr
1 5

<210> 65
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<220>
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<400> 65
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ccaggcaagg ggctggagtg ggtgggagtt atatggtctg atggaagtga taaaaagtat 180

gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

cttcttatga acagcctgag agacgatgac acggctgtgt atcactgtgc gagagagggg 300

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gtctcctca 369

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

<220>
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<400> 66

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20   25   30

Gly Met His Trp Phe Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Gly Val Ile Trp Ser Asp Gly Ser Asp Lys Lys Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80

Leu Leu Met Asn Ser Leu Arg Asp Asp Asp Thr Ala Val Tyr His Cys
                85   90   95

Ala Arg Glu Gly Gly Phe Leu Tyr Ser Ser Ser Ser His Phe Asp Tyr
            100   105   110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 67
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
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<400> 67
ggattcacct tcagtagcta tggc   24

<210> 68
<211> 8
<212> PRT
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<220>
<223> synthetic

<400> 68

Gly Phe Thr Phe Ser Ser Tyr Gly

1 5

<210> 69
<211> 24
<212> DNA
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<220>
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<400> 69
atatggtctg atggaagtga taaa 24

<210> 70
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<400> 70

Ile Trp Ser Asp Gly Ser Asp Lys
1 5

<210> 71
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<212> DNA
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<400> 71
gcgagagagg gggggttcct ttatagcagc tcgtcccact ttgactac 48

<210> 72
<211> 16
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<220>
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<400> 72

Ala Arg Glu Gly Gly Phe Leu Tyr Ser Ser Ser Ser His Phe Asp Tyr

1 5 10 15

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gggaaagccc ctaaactcct gatctttgct gcatccagtt tacaaagtgg ggtcccatca 180

aggttcagcg gcagtggatc tggcacagat ttcactctca ccatcagcag cctgcagcct 240

gaagattttg caatttatta ctgtctacaa gattacaagt acccattcac tttcggcgga 300

gggaccaagg tggagatcaa a 321

<210> 74
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<212> PRT
<213> Artificial Sequence

<220>
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<400> 74

Ala Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Thr Ser Gln Gly Ile Arg Asn Asp
20 25 30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Phe Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro

65 70 75 80

Glu Asp Phe Ala Ile Tyr Tyr Cys Leu Gln Asp Tyr Lys Tyr Pro Phe
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 75
<211> 18
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<400> 75
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<210> 76
<211> 6
<212> PRT
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<220>
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<400> 76

Gln Gly Ile Arg Asn Asp
1 5

<210> 77
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
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<400> 77
gctgcatcc 9

<210> 78
<211> 3
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<400> 78

Ala Ala Ser
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<210> 79
<211> 27
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<400> 79
ctacaagatt acaagtaccc attcact 27

<210> 80
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<400> 80

Leu Gln Asp Tyr Lys Tyr Pro Phe Thr
1 5

<210> 81
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tcctgtgcag cctctgggtt caccttcagt tcctatggcc tgcactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcagtt atatcagatg atggaagtta taaattctat 180

gcagactcca tgaagggccg attcaccatc tctagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agctgaggac acggctgtgt attactgtgc gaaagatcgg 300

ggtcgcagtg gctggtacta ctttgactac tggggccagg gaaccctggt cactgtctcc 360

tca 363

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<400> 82

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Leu His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Ser Asp Asp Gly Ser Tyr Lys Phe Tyr Ala Asp Ser Met
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

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

Ala Lys Asp Arg Gly Arg Ser Gly Trp Tyr Tyr Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 83

<211> 24
<212> DNA
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<400> 83
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<210> 84
<211> 8
<212> PRT
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<220>
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<400> 84

Gly Phe Thr Phe Ser Ser Tyr Gly
1 5

<210> 85
<211> 24
<212> DNA
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<400> 85
atatcagatg atggaagtta taaa 24

<210> 86
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<400> 86

Ile Ser Asp Asp Gly Ser Tyr Lys
1 5

<210> 87

<211> 42
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<400> 87
gcgaaagatc ggggtcgcag tggctggtac tactttgact ac 42

<210> 88
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<400> 88

Ala Lys Asp Arg Gly Arg Ser Gly Trp Tyr Tyr Phe Asp Tyr
1 5 10

<210> 89
<211> 321
<212> DNA
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<400> 89
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atcacttgcc gggccagtca gagtattagt agctggttgg cctggtatca gcagaaacca 120

gggaaagccc ctaagctcct gatctataag gcgtctagtt tagaaagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagaa ttcactctca ccatcagcag cctgcagcct 240

gatgattttg caacttatta ctgccaacag tatgatagtt attctcggac gttcggccaa 300

gggaccaagg tggaaatcaa a 321

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<211> 107
<212> PRT
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<220>
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<400> 90

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Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1               5                  10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Trp
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asp Ser Tyr Ser Arg
                85                  90                  95


Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105
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<211> 18
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<220>
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<400> 91
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<210> 92
<211> 6
<212> PRT
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<220>
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<400> 92

Gln Ser Ile Ser Ser Trp
1 5

<210> 93
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
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<400> 93
aaggcgtct 9

<210> 94
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<400> 94

Lys Ala Ser
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<210> 95
<211> 27
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<400> 95
caacagtatg atagttattc tcggacg 27

<210> 96
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<400> 96

Gln Gln Tyr Asp Ser Tyr Ser Arg Thr
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<210> 97
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tcctgtgcag cctctggatt caccttcagt agttatgaaa tgaactgggt ccgccaggct 120

ccagggaagg gtctggagtg ggtttcattc attagtgata gtagtagtaa catatactac 180

gcagactctg tgaagggccg attcaccatc tccagagaca atgccaagaa gtcactgtat 240

cttcaaatga ccagcctgag ggccgaggac acggctgttt attactgtgc gagagaagcc 300

attggcagca cctcctttga caactggggc cagggaaccc tggtcaccgt ctcctca 357

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<211> 119
<212> PRT
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<220>
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<400> 98

Glu Val Gln Leu Val Glu Ser Gly Gly Asp Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Glu Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Phe Ile Ser Asp Ser Ser Ser Asn Ile Tyr Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Lys Ser Leu Tyr
65 70 75 80

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

Ala Arg Glu Ala Ile Gly Ser Thr Ser Phe Asp Asn Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

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<210> 100
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Gly Phe Thr Phe Ser Ser Tyr Glu
1 5

<210> 101
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<400> 101
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<210> 102
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<400> 102

Ile Ser Asp Ser Ser Ser Asn Ile
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<210> 103
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<210> 104
<211> 12
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Ala Arg Glu Ala Ile Gly Ser Thr Ser Phe Asp Asn
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<220>
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<400> 105
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ctctcctgca gggccagtca gagtgttagc agcagtttag cctggtacca gcagaaacct 120

ggccaggctc ccaggcgcct catctatagt gcatccacca gggccactgg tatcccagcc 180

aggttcagtg gcagtgggtc tgggacagag ttcactctca ccatcagcag cctgcagtct 240

gaagattttg caatttatta ctgtcatcaa tataataact ggcctctcac tttcggcgga 300

gggaccaagg tggagatcaa a 321

<210> 106
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<220>
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<400> 106

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1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Arg Leu Ile
35 40 45

Tyr Ser Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80

Glu Asp Phe Ala Ile Tyr Tyr Cys His Gln Tyr Asn Asn Trp Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 107
<211> 18
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<400> 107
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<210> 108
<211> 6
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Gln Ser Val Ser Ser Ser
1 5

<210> 109
<211> 9
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agtgcatcc 9

<210> 110
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<212> PRT
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<400> 110

Ser Ala Ser
1

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<211> 27
<212> DNA
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<400> 111
catcaatata ataactggcc tctcact 27

<210> 112
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<400> 112

His Gln Tyr Asn Asn Trp Pro Leu Thr
1 5

<210> 113
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
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<400> 113
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tcctgtgcag cctctgggtt caccgtcagt agcaactcca tgagctgggt ccgccaggct 120

ccaggggagg ggctggagtg ggtctcagtt atttttagcg gtggtatcac atactactca 180

gactccgtga agggccgatt caccatctcc agacacaatt ccaagaacac gctgtatctt 240

caaatgaaca gcctgagaac tgaggacacg gccgtatatt actgtgcgcg tcattctaac 300

tggaactttg atgcttttga tatctggggc caagggacaa tggtcaccgt ctcttca 357

<210> 114
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<212> PRT

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<220>
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<400> 114

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Ser Ser Asn
20 25 30

Ser Met Ser Trp Val Arg Gln Ala Pro Gly Glu Gly Leu Glu Trp Val
35 40 45

Ser Val Ile Phe Ser Gly Gly Ile Thr Tyr Tyr Ser Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg His Asn Ser Lys Asn Thr Leu Tyr Leu
65 70 75 80

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

Arg His Ser Asn Trp Asn Phe Asp Ala Phe Asp Ile Trp Gly Gln Gly
100 105 110

Thr Met Val Thr Val Ser Ser
115

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<210> 116

<211> 8
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<400> 116

Gly Phe Thr Val Ser Ser Asn Ser
1 5

<210> 117
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<400> 117
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<210> 118
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<400> 118

Ile Phe Ser Gly Gly Ile Thr
1 5

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<210> 120

<211> 13
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<400> 120

Ala Arg His Ser Asn Trp Asn Phe Asp Ala Phe Asp Ile
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<211> 321
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<220>
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<400> 121
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atcacttgcc gggcaagtca gagctttgac acctatttaa attggtatca gcagaaacca 120

gggaaagccc ctaacctcct gatctatgct acatccagtt tgcaaagtgg ggtcccatca 180

aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240

gaagattttg gaacttacta ttgtcaacag agttacagta tcccgtacac ttttggccag 300

gggaccaagc tggagatcaa a 321

<210> 122
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
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<400> 122

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Phe Asp Thr Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Asn Leu Leu Ile
35 40 45

Tyr Ala Thr Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Gly Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Ile Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 123
<211> 18
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<220>
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<400> 123
cagagctttg acacctat 18

<210> 124
<211> 6
<212> PRT
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<220>
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<400> 124

Gln Ser Phe Asp Thr Tyr
1 5

<210> 125
<211> 9
<212> DNA
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<400> 125
gctacatcc 9

<210> 126
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<400> 126

Ala Thr Ser
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<400> 127
caacagagtt acagtatccc gtacact 27

<210> 128
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<400> 128

Gln Gln Ser Tyr Ser Ile Pro Tyr Thr
1 5

<210> 129
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tcctgcaagg cttctggata caccttcacc ggctactatc tacactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggattg atcaacccta atactggtgg cacaaacttt 180

gcacagaaat ttcagggcag ggtcaccatg accagggact cgtcaatcag cgcagcctac 240

atggaactga gcaggctgag atctgacgac acggccgtgt attactgtgc gagacaacac 300

tggaaccgtt attttgacaa ctggggccag ggaaccctgg tcaccgtctc ctca 354

<210> 130
<211> 118
<212> PRT
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<220>
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<400> 130

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1 5 10 15

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

Tyr Leu His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Leu Ile Asn Pro Asn Thr Gly Gly Thr Asn Phe Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Ser Ser Ile Ser Ala Ala Tyr
65 70 75 80

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

Ala Arg Gln His Trp Asn Arg Tyr Phe Asp Asn Trp Gly Gln Gly Thr

100 105 110

Leu Val Thr Val Ser Ser
115

<210> 131
<211> 24
<212> DNA
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<400> 131
ggatacacct tcaccggcta ctat 24

<210> 132
<211> 8
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<220>
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<400> 132

Gly Tyr Thr Phe Thr Gly Tyr Tyr
1 5

<210> 133
<211> 24
<212> DNA
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<400> 133
atcaacccta atactggtgg caca 24

<210> 134
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<220>
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<400> 134

Ile Asn Pro Asn Thr Gly Gly Thr
1 5

<210> 135
<211> 33
<212> DNA
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<400> 135
gcgagacaac actggaaccg ttattttgac aac 33

<210> 136
<211> 11
<212> PRT
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<400> 136

Ala Arg Gln His Trp Asn Arg Tyr Phe Asp Asn
1 5 10

<210> 137
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
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<400> 137
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atcacttgcc gggccagtca gagtgttggt aactggttgg cctggtatca gcagaaacca 120

gggaaagccc ctaaactcct gatccaagag gcgtccagta tagaaagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagaa ttcactctta tcgtcagcag cctgcagcct 240

gatgattttg caacttatta ctgccaacag tataatagtt attcgtggac gttcggccac 300

gggaccaagg tggaaatcaa a 321

<210> 138
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 138

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Val Gly Asn Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Gln Glu Ala Ser Ser Ile Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Ile Val Ser Ser Leu Gln Pro
65 70 75 80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Ser Trp
85 90 95

Thr Phe Gly His Gly Thr Lys Val Glu Ile Lys
100 105

<210> 139
<211> 18
<212> DNA
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<220>
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<400> 139
cagagtgttg gtaactgg 18

<210> 140
<211> 6
<212> PRT
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<220>
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<400> 140

Gln Ser Val Gly Asn Trp
1 5

<210> 141
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
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<400> 141
gaggcgtcc 9

<210> 142
<211> 3
<212> PRT
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<220>
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<400> 142

Glu Ala Ser
1

<210> 143
<211> 27
<212> DNA
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<220>
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<400> 143
caacagtata atagttattc gtggacg 27

<210> 144
<211> 9
<212> PRT
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<220>
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<400> 144

Gln Gln Tyr Asn Ser Tyr Ser Trp Thr
1 5

<210> 145
<211> 348
<212> DNA
<213> Artificial Sequence

<220>
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<400> 145
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acctgctctg tctctggtgg ctccatcact aattacttct ggacctggat ccggcagtcc 120

ccagggaagg gactggaatg gattgggtat atctattaca gtgggggcac caactataac 180

ccctccctca agagtcgagt caccatatca atagacacgt ccaagaacca attctccctg 240

aatatgaatt ctgtgaccgc tgcggacacg gccgtctatt actgtgcggg gagctactac 300

tacggtgtgg acgtctgggg ccaagggacc acggtcaccg tctcctca 348

<210> 146
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 146

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Ser Val Ser Gly Gly Ser Ile Thr Asn Tyr

20 25 30

Phe Trp Thr Trp Ile Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Tyr Tyr Ser Gly Gly Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

Ser Arg Val Thr Ile Ser Ile Asp Thr Ser Lys Asn Gln Phe Ser Leu
65 70 75 80

Asn Met Asn Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Gly Ser Tyr Tyr Tyr Gly Val Asp Val Trp Gly Gln Gly Thr Thr Val
100 105 110

Thr Val Ser Ser
115

<210> 147
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 147
ggtggctcca tcactaatta cttc 24

<210> 148
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 148

Gly Gly Ser Ile Thr Asn Tyr Phe
1 5

<210> 149
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 149
atctattaca gtgggggcac c 21

<210> 150
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 150

Ile Tyr Tyr Ser Gly Gly Thr
1 5

<210> 151
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 151
gcggggagct actactacgg tgtggacgtc 30

<210> 152
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 152

Ala Gly Ser Tyr Tyr Tyr Gly Val Asp Val
1 5 10

<210> 153
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
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<400> 153
gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 60

ctctcctgca gggccagtca gagtattaaa agcttcttag cctggtaccg acagaaacct 120

ggccaggctc ccagactcct catctatgat gcatccaaca ggcccactgg catcccagcc 180

aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatcaacag cctagagtct 240

gaagattttg cagtttattt ctgtcagcag cgtaacaact ggccattcac tttcggccct 300

gggaccaaag tggatatcaa a 321

<210> 154
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 154

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Lys Ser Phe
20 25 30

Leu Ala Trp Tyr Arg Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Pro Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Leu Glu Ser
65 70 75 80

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Arg Asn Asn Trp Pro Phe
85 90 95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> 155
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 155
cagagtatta aaagcttc 18

<210> 156
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 156

Gln Ser Ile Lys Ser Phe
1 5

<210> 157
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 157
gatgcatcc 9

<210> 158
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 158

Asp Ala Ser
1

<210> 159
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 159
cagcagcgta acaactggcc attcact 27

<210> 160
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
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<400> 160

Gln Gln Arg Asn Asn Trp Pro Phe Thr
1 5

<210> 161
<211> 375
<212> DNA
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<220>
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<400> 161
caggtgcagc tggtggagtc tgggggaggc ttggtcaagc ctggagggtc cctgagactc 60

tcctgtgcag cctctggatt caccttcagt gactactaca tgaactggat ccgccaggct 120

ccaggaaagg ggctagagtg gatttcactc attagtagta gtggtagtgc catatattac 180

tcagactctg tgaagggccg attcaccata tccagggaca atgccaggaa atcactgtat 240

ctgcaagtga acagcctgag agccgaggac acggccgtat attactgtgc gagagatcgg 300

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gtcaccgtct cctca 375

<210> 162
<211> 125
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 162

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Tyr Met Asn Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Ser Leu Ile Ser Ser Ser Gly Ser Ala Ile Tyr Tyr Ser Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Lys Ser Leu Tyr
65 70 75 80

Leu Gln Val Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Arg Gly Glu Trp Ala Leu Gly Ala Tyr Tyr Tyr Gly Leu
100 105 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 163
<211> 24
<212> DNA

<213> Artificial Sequence

<220>
<223> synthetic

<400> 163
ggattcacct tcagtgacta ctac 24

<210> 164
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 164

Gly Phe Thr Phe Ser Asp Tyr Tyr
1 5

<210> 165
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 165
attagtagta gtggtagtgc cata 24

<210> 166
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 166

Ile Ser Ser Ser Gly Ser Ala Ile
1 5

<210> 167
<211> 54
<212> DNA

<213> Artificial Sequence

<220>
<223> synthetic

<400> 167
gcgagagatc ggggggagtg ggccctcgga gcctactact acggtttgga cgtc 54

<210> 168
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<400> 168

Ala Arg Asp Arg Gly Glu Trp Ala Leu Gly Ala Tyr Tyr Tyr Gly Leu
1 5 10 15

Asp Val

<210> 169
<211> 336
<212> DNA
<213> Artificial Sequence

<220>
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<400> 169
gatattgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc 60

atctcctgca ggtctagtca gagcctccta catagtgatg gatacaacta tttggattgg 120

tacctgcaga agtcagggca gtctccacag ctcctgatct atttgggttc taatcgggcc 180

tccggggtcc ctgacaggtt cagtggcagt ggatcaggca cagattttac actgaaaatc 240

agcagaatgg aggctgagga tgttggggtt tattactgca tgcaagctct acaaactccg 300

tacacttttg gccaggggac caagctggag atcaaa 336

<210> 170
<211> 112
<212> PRT

<213> Artificial Sequence

<220>
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<400> 170

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asp Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Ser Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Met Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
85 90 95

Leu Gln Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 171
<211> 33
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 171
cagagcctcc tacatagtga tggatacaac tat 33

<210> 172
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 172

Gln Ser Leu Leu His Ser Asp Gly Tyr Asn Tyr
1 5 10

<210> 173
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 173
ttgggttct 9

<210> 174
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
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<400> 174

Leu Gly Ser
1

<210> 175
<211> 27
<212> DNA
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<220>
<223> synthetic

<400> 175
atgcaagctc tacaaactcc gtacact 27

<210> 176
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 176

Met Gln Ala Leu Gln Thr Pro Tyr Thr
1 5

<210> 177
<211> 375
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 177
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc 60

acctgcactg tctctggtgg ctccatcagc agtgctgatc actactggag ctggatccgc 120

cagcagccag ggaagggcct ggaatggatt gggtacattt cttatagagg gacaacctac 180

tacaacccga ccctcgagag tcgtgttagc atttcagtag acacgtttaa gaatcaattc 240

tccctgatgt tgcactccgt gactgtcgcg gacacggccg tgtattattg tgcgaaagta 300

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gtcaccgtct cctca 375

<210> 178
<211> 125
<212> PRT
<213> Artificial Sequence

<220>
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<400> 178

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Ala
20 25 30

Asp His Tyr Trp Ser Trp Ile Arg Gln Gln Pro Gly Lys Gly Leu Glu

35 40 45

Trp Ile Gly Tyr Ile Ser Tyr Arg Gly Thr Thr Tyr Tyr Asn Pro Thr
50 55 60

Leu Glu Ser Arg Val Ser Ile Ser Val Asp Thr Phe Lys Asn Gln Phe
65 70 75 80

Ser Leu Met Leu His Ser Val Thr Val Ala Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Ala Lys Val Leu Gln Gly Leu Val Arg Phe Arg Asp Tyr Gly Phe
100 105 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 179
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 179
ggtggctcca tcagcagtgc tgatcactac 30

<210> 180
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
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<400> 180

Gly Gly Ser Ile Ser Ser Ala Asp His Tyr
1 5 10

<210> 181
<211> 21
<212> DNA

<213> Artificial Sequence

<220>
<223> synthetic

<400> 181
atttcttata gagggacaac c 21

<210> 182
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 182

Ile Ser Tyr Arg Gly Thr Thr
1 5

<210> 183
<211> 51
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 183
gcgaaagtac tccaagggct cgtcagattc agggactacg gtttcgacgt c 51

<210> 184
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 184

Ala Lys Val Leu Gln Gly Leu Val Arg Phe Arg Asp Tyr Gly Phe Asp
1 5 10 15

Val

<210> 185
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 185
gacatccagt tgacccagtc tccacccttc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgct gggccagtca ggacattagc agttatttag cctggtatca gcaaaatccc 120

gggaaatccc ctaaactcct gatctatgat gcttttactt tacacactgg ggtcccatca 180

aggtttagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240

gaggattttg caacttttta ctgtcaacac ctttatagtt ttccattcac tttcggccct 300

gggaccaaag tggatatcaa a 321

<210> 186
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
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<400> 186

Asp Ile Gln Leu Thr Gln Ser Pro Pro Phe Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Trp Ala Ser Gln Asp Ile Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Asn Pro Gly Lys Ser Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Phe Thr Leu His Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Phe Tyr Cys Gln His Leu Tyr Ser Phe Pro Phe
85 90 95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> 187
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
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<400> 187
caggacatta gcagttat 18

<210> 188
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
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<400> 188

Gln Asp Ile Ser Ser Tyr
1 5

<210> 189
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 189
gatgctttt 9

<210> 190
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 190

Asp Ala Phe
1

<210> 191
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 191
caacaccttt atagttttcc attcact 27

<210> 192
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 192

Gln His Leu Tyr Ser Phe Pro Phe Thr
1 5

<210> 193
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
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<400> 193
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tcctgtgcag cctctggatt cacctttagg aattatgcca tgcactgggt ccgacaagct 120

ccaggggagg gcctggagtg ggtcgcagcc atttatcgga atagtgattc catagactat 180

gcggactctg tgaagggccg attcaccatt tccagagaca acgccaagaa ctccctatat 240

ctgcaaatga acagtctgaa aactgaggac acggcgttgt attactgtgc aaaagatgag 300

ggatttttgg agtactttga ctcctggggc cagggaaccc tggtcaccgt ctcctca 357

<210> 194
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
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<400> 194

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Arg Asn Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Glu Gly Leu Glu Trp Val
35 40 45

Ala Ala Ile Tyr Arg Asn Ser Asp Ser Ile Asp Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Ala Lys Asp Glu Gly Phe Leu Glu Tyr Phe Asp Ser Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 195
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
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<400> 195
ggattcacct ttaggaatta tgcc 24

<210> 196
<211> 8
<212> PRT
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<220>
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<400> 196

Gly Phe Thr Phe Arg Asn Tyr Ala
1 5

<210> 197
<211> 24
<212> DNA
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<220>
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<400> 197
atttatcgga atagtgattc cata 24

<210> 198
<211> 8
<212> PRT
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<220>
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<400> 198

Ile Tyr Arg Asn Ser Asp Ser Ile
1 5

<210> 199
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
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<400> 199
gcaaaagatg agggattttt ggagtacttt gactcc 36

<210> 200
<211> 12
<212> PRT
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<220>
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<400> 200

Ala Lys Asp Glu Gly Phe Leu Glu Tyr Phe Asp Ser
1 5 10

<210> 201
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
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<400> 201
gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagcctcc 60

ctctcctgca gggccagtca gagtgttagc agcagcttct tagcctggta ccagcagaaa 120

cctggccagg ctcccaggct cctcatctac ggtgtatcca gcaggttcat tggcatccca 180

gacaggttca gtggcggtgg gtctgggaca gacttcactc tcaccatcac cagactggag 240

cctgaagatt ttgcagtgta ttactgtcag cagtatggta ggtcaccgtg gacgttcggc 300

caagggacca aggtggaaat caaa 324

<210> 202
<211> 108
<212> PRT
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<220>
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<400> 202

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Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1               5                  10                  15


Glu Arg Ala Ser Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
            20                  25                  30


Phe Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35                  40                  45


Ile Tyr Gly Val Ser Ser Arg Phe Ile Gly Ile Pro Asp Arg Phe Ser
    50                  55                  60


Gly Gly Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Thr Arg Leu Glu
65                  70                  75                  80


Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Arg Ser Pro
                85                  90                  95


Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210>  203
<211>  21
<212>  DNA
<213>  Artificial Sequence

<220>
<223>  synthetic

<400>  203
cagagtgtta gcagcagctt c                                                21


<210>  204
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<212>  PRT
<213>  Artificial Sequence

<220>
<223>  synthetic

<400>  204

Gln Ser Val Ser Ser Ser Phe
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1 5

<210> 205
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 205
ggtgtatcc 9

<210> 206
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 206

Gly Val Ser
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<210> 207
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<212> DNA
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<220>
<223> synthetic

<400> 207
cagcagtatg gtaggtcacc gtggacg 27

<210> 208
<211> 9
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<220>
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<400> 208

Gln Gln Tyr Gly Arg Ser Pro Trp Thr

1 5

<210> 209
<211> 366
<212> DNA
<213> Artificial Sequence

<220>
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<400> 209
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ccaggcaagg gactggaatg ggtggcagtt atatcatatg atggagatga taaatactat 180

ggagactccg tgaagggccg attcaccatt tccagagaca attccaagac catggtgtat 240

ctgcacatga acagcctgag aactgaggac acggctgtgt attattgtgc gaaagatgga 300

tatagtctct acgggaagga ctactttgac tattggggcc agggaaccct ggtcaccgtc 360

tcctca 366

<210> 210
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 210

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
20 25 30

Ala Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Ser Tyr Asp Gly Asp Asp Lys Tyr Tyr Gly Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Thr Met Val Tyr
65 70 75 80

Leu His Met Asn Ser Leu Arg Thr Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Gly Tyr Ser Leu Tyr Gly Lys Asp Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 211
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 211
ggattcacct tcagtagata tgcc 24

<210> 212
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 212

Gly Phe Thr Phe Ser Arg Tyr Ala
1 5

<210> 213
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 213

atatcatatg atggagatga taaa 24

<210> 214
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 214

Ile Ser Tyr Asp Gly Asp Asp Lys
1 5

<210> 215
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 215
gcgaaagatg gatatagtct ctacgggaag gactactttg actat 45

<210> 216
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 216

Ala Lys Asp Gly Tyr Ser Leu Tyr Gly Lys Asp Tyr Phe Asp Tyr
1 5 10 15

<210> 217
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 217

gaaattgtgt tgacacagtc tccaggcacc ctgcctttgt ctccagggga aagagccacc 60

ctctcctgca gggccagtca gagtattacc aacagctact tagcctggta ccagcagaaa 120

cctgaccagg ctcccagact cctcatctat ggtgcgtcca gcagggccac tggcatccca 180

gacaggttca gtggcagtga gtctgggaca gactttactc tcaccatcag cagactggag 240

cctgaagatt ttgcagtgta ttactgtcag cagtatgtta ggtcaccgtg gacgttcggc 300

caagggacca aggtggaaat caaa 324

<210> 218
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 218

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Pro Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Thr Asn Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Asp Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Glu Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Val Arg Ser Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 219

<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 219
cagagtatta ccaacagcta c 21

<210> 220
<211> 7
<212> PRT
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<220>
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<400> 220

Gln Ser Ile Thr Asn Ser Tyr
1 5

<210> 221
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 221
ggtgcgtcc 9

<210> 222
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 222

Gly Ala Ser
1

<210> 223

<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 223
cagcagtatg ttaggtcacc gtggacg 27

<210> 224
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 224

Gln Gln Tyr Val Arg Ser Pro Trp Thr
1 5

<210> 225
<211> 363
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 225
caggtgcagc tacagcagtg gggcgcagga ctgttgaagc cctcggagac cctgtccctc 60

acctgcgttg tctatggtga gtctttcggt aattaccatt ggaattggat ccgccagtcc 120

ccagggaagc ggctggagtg gattggggaa atcaatcaaa atggacacac caattacaac 180

ccgtccctca agagtcgagt caccatatca gtggacacgt ccaagatcca attttccctg 240

agactgaact ctgtgaccgc cgcggacacg gctgtgtatt tctgtgcgag aggccataac 300

tacgtaaatt cctacttcgg tttggacgtc tggggccaag ggaccacggt caccgtctcc 360

tca 363

<210> 226
<211> 121
<212> PRT

<213> Artificial Sequence

<220>
<223> synthetic

<400> 226

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

Thr Leu Ser Leu Thr Cys Val Val Tyr Gly Glu Ser Phe Gly Asn Tyr
20 25 30

His Trp Asn Trp Ile Arg Gln Ser Pro Gly Lys Arg Leu Glu Trp Ile
35 40 45

Gly Glu Ile Asn Gln Asn Gly His Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Ile Gln Phe Ser Leu
65 70 75 80

Arg Leu Asn Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Phe Cys Ala
85 90 95

Arg Gly His Asn Tyr Val Asn Ser Tyr Phe Gly Leu Asp Val Trp Gly
100 105 110

Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 227
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 227
ggtgagtctt tcggtaatta ccat 24

<210> 228

<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 228

Gly Glu Ser Phe Gly Asn Tyr His
1 5

<210> 229
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 229
atcaatcaaa atggacacac c 21

<210> 230
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
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<400> 230

Ile Asn Gln Asn Gly His Thr
1 5

<210> 231
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 231
gcgagaggcc ataactacgt aaattcctac ttcggtttgg acgtc 45

<210> 232

<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 232

Ala Arg Gly His Asn Tyr Val Asn Ser Tyr Phe Gly Leu Asp Val
1 5 10 15

<210> 233
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 233
gaaattgtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc 60

ctctcctgca ggaccagtca gagtgtaagc atcagcttag cctggtacca gcggaaacct 120

ggccaggctc ccaggctcct catctttggt tcatccacca gggccactgg tgtcccagcc 180

aggttcagtg gcagtgggtc tgggacagag ttcactctca ccatcagcag cctgcagtct 240

gaagattttg cagtttatta ctgtcagcag tataataact ggccgtacac ttttggccag 300

gggaccaagc tggagatcaa a 321

<210> 234
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 234

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Thr Ser Gln Ser Val Ser Ile Ser
20 25 30

Leu Ala Trp Tyr Gln Arg Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Phe Gly Ser Ser Thr Arg Ala Thr Gly Val Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Asn Trp Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 235
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 235
cagagtgtaa gcatcagc 18

<210> 236
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 236

Gln Ser Val Ser Ile Ser
1 5

<210> 237
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 237
ggttcatcc 9

<210> 238
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 238

Gly Ser Ser
1

<210> 239
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 239
cagcagtata ataactggcc gtacact 27

<210> 240
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
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<400> 240

Gln Gln Tyr Asn Asn Trp Pro Tyr Thr
1 5

<210> 241
<211> 360
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 241
caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg cttctggata caccttcgcc gcccactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggatgg atcaacactt acactggtgg cacaaactat 180

gggcagaagt ttcagggcag ggtcaccatg accagggaca cgtccatcac cacagcctac 240

atggagctga gcaggctgag atctgacgac acggccgttt attactgtgc gcgagatcgg 300

cggaactgga acttcgtctt tgaatattgg ggccagggaa ccctggtcac cgtctcctca 360

<210> 242
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 242

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

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

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Gly Thr Asn Tyr Gly Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Thr Thr Ala Tyr
65 70 75 80

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

Ala Arg Asp Arg Arg Asn Trp Asn Phe Val Phe Glu Tyr Trp Gly Gln

100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 243
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 243
ggatacacct tcgccgccca ctat 24

<210> 244
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 244

Gly Tyr Thr Phe Ala Ala His Tyr
1 5

<210> 245
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 245
atcaacactt acactggtgg caca 24

<210> 246
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 246

Ile Asn Thr Tyr Thr Gly Gly Thr
1 5

<210> 247
<211> 39
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 247
gcgcgagatc ggcggaactg gaacttcgtc tttgaatat 39

<210> 248
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 248

Ala Arg Asp Arg Arg Asn Trp Asn Phe Val Phe Glu Tyr
1 5 10

<210> 249
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 249
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcagttgcc gggcaagtca gaacattaag aactatttaa attggtatca gcagaaacca 120

gggaaagccc ctaaactcct gatctatgaa gcatctaatt tgcaaagtgg ggccccatca 180

aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctggaacct 240

gaagattttg caacttacta ctgtcaacag agttttagta ttccgtggac gttcggccaa 300

gggaccaagg tggaaatcaa a 321

<210> 250
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 250

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asn Ile Lys Asn Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Glu Ala Ser Asn Leu Gln Ser Gly Ala Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Phe Ser Ile Pro Trp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 251
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 251
cagaacatta agaactat 18

<210> 252
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 252

Gln Asn Ile Lys Asn Tyr
1 5

<210> 253
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 253
gaagcatct 9

<210> 254
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 254

Glu Ala Ser
1

<210> 255
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 255
caacagagtt ttagtattcc gtggacg 27

<210> 256
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 256

Gln Gln Ser Phe Ser Ile Pro Trp Thr
1 5

<210> 257
<211> 366
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 257
caggtgcagc tggtgcagtc tggggctgaa gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg cttctggata caccttcatc gcctactatt tacactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggattg ctcaaccctt atactggtgg ctcatactat 180

acacagaagt ttcagggcag ggtcaccatg accagggaca cgtccatcga cacagcctac 240

atggaactga acagtctgag atctgacgac acggccatct attactgtgc gagagataag 300

aggagctact acatccctta tgcttttgaa atctggggcc aagggacaat ggtcaccgtc 360

tcttca 366

<210> 258
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 258

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

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


Tyr Leu His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45


Gly Leu Leu Asn Pro Tyr Thr Gly Gly Ser Tyr Tyr Thr Gln Lys Phe
    50                  55                  60


Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Asp Thr Ala Tyr
65                  70                  75                  80


Met Glu Leu Asn Ser Leu Arg Ser Asp Asp Thr Ala Ile Tyr Tyr Cys
                85                  90                  95


Ala Arg Asp Lys Arg Ser Tyr Tyr Ile Pro Tyr Ala Phe Glu Ile Trp
            100                 105                 110


Gly Gln Gly Thr Met Val Thr Val Ser Ser
        115                 120


<210>  259
<211>  24
<212>  DNA
<213>  Artificial Sequence

<220>
<223>  synthetic

<400>  259
ggatacacct tcatcgccta ctat                                              24


<210>  260
<211>  8
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  synthetic

<400>  260

Gly Tyr Thr Phe Ile Ala Tyr Tyr
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1 5

<210> 261
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 261
ctcaaccctt atactggtgg ctca 24

<210> 262
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 262

Leu Asn Pro Tyr Thr Gly Gly Ser
1 5

<210> 263
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 263
gcgagagata agaggagcta ctacatccct tatgcttttg aaatc 45

<210> 264
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 264

Ala Arg Asp Lys Arg Ser Tyr Tyr Ile Pro Tyr Ala Phe Glu Ile

1 5 10 15

<210> 265
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 265
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcaagtca gagcattagc agctatttaa attggtatca gcagaaacca 120

gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccgtca 180

aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240

gaagattttg caacttacta ctgtcaacag agttacagta cccctccgat caccttcggc 300

caagggacac gactggagat taaa 324

<210> 266
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 266

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro

65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Pro
85 90 95

Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 267
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
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<400> 267
cagagcatta gcagctat 18

<210> 268
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 268

Gln Ser Ile Ser Ser Tyr
1 5

<210> 269
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
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<400> 269
gctgcatcc 9

<210> 270
<211> 3
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<220>
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<400> 270

Ala Ala Ser
1

<210> 271
<211> 30
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<220>
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<400> 271
caacagagtt acagtacccc tccgatcacc 30

<210> 272
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
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<400> 272

Gln Gln Ser Tyr Ser Thr Pro Pro Ile Thr
1 5 10

<210> 273
<211> 369
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 273
gaggtgcagc tggtggagtc tgggggaggc ttggttcagc ctggggtgtc cctgagactc 60

tcctgtgtag cctctggatt cacctttagc aattatgaca taacctggat ccgccagatt 120

ccagggaagg ggctggagtg ggtctcaaga atcagtggta gtggtggaag tacatatttc 180

gcagactccg tgaagggtcg gttcatcatc tccagagaca attccaaaaa tacggtgtat 240

atgcaaatga acagtttgag agccgaagac tcggccgtat attactgtgc gagaagagat 300

tccgtcttat ttagtatgaa cagttggctc gacccctggg gccagggaac cctggtcacc 360

gtctcctca 369

<210> 274
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 274

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Val
1 5 10 15

Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Asp Ile Thr Trp Ile Arg Gln Ile Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Arg Ile Ser Gly Ser Gly Gly Ser Thr Tyr Phe Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr
65 70 75 80

Met Gln Met Asn Ser Leu Arg Ala Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Asp Ser Val Leu Phe Ser Met Asn Ser Trp Leu Asp Pro
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 275

<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 275
ggattcacct ttagcaatta tgac 24

<210> 276
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 276

Gly Phe Thr Phe Ser Asn Tyr Asp
1 5

<210> 277
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 277
atcagtggta gtggtggaag taca 24

<210> 278
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 278

Ile Ser Gly Ser Gly Gly Ser Thr
1 5

<210> 279

<211> 48
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 279
gcgagaagag attccgtctt atttagtatg aacagttggc tcgacccc 48

<210> 280
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 280

Ala Arg Arg Asp Ser Val Leu Phe Ser Met Asn Ser Trp Leu Asp Pro
1 5 10 15

<210> 281
<211> 369
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 281
gaggtgcagc tggtgcagtc tggagcagag gtgaaaaagc ccggggagtc tctgaagatc 60

tcctgttcgg gatctggata caggtttacc aactactgga tcgcctgggt gcgccagatg 120

cccgggaaag gcctggagtg gatgggtctc attcatcctg atgactctga tattagatac 180

agcccgtcct tccaaggcca ggtcaccttt tcagtcgaca agtccatcaa caccgcctac 240

ctgcagtgga gcagcctgaa ggcctcggac accgccatgt attactgtac gcgacaagac 300

ggaatactat ggtctcataa tgcctggttc gacccctggg gccagggaac cctggtcacc 360

gtctcctca 369

<210> 282
<211> 123
<212> PRT

<213> Artificial Sequence

<220>
<223> synthetic

<400> 282

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

Ser Leu Lys Ile Ser Cys Ser Gly Ser Gly Tyr Arg Phe Thr Asn Tyr
20 25 30

Trp Ile Ala Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Leu Ile His Pro Asp Asp Ser Asp Ile Arg Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Phe Ser Val Asp Lys Ser Ile Asn Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Thr Arg Gln Asp Gly Ile Leu Trp Ser His Asn Ala Trp Phe Asp Pro
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 283
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 283
ggatacaggt ttaccaacta ctgg 24

<210> 284

<211> 8
<212> PRT
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<220>
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<400> 284

Gly Tyr Arg Phe Thr Asn Tyr Trp
1 5

<210> 285
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 285
attcatcctg atgactctga tatt 24

<210> 286
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 286

Ile His Pro Asp Asp Ser Asp Ile
1 5

<210> 287
<211> 48
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 287
acgcgacaag acggaatact atggtctcat aatgcctggt tcgacccc 48

<210> 288

<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 288

Thr Arg Gln Asp Gly Ile Leu Trp Ser His Asn Ala Trp Phe Asp Pro
1 5 10 15

<210> 289
<211> 360
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 289
caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg cctctggata caccttcatt agttacaata tcttctgggt gcgacaggcc 120

actggtcagg gccttgattg gatgggatgg atgaacccct tcagaaataa cgcaggttat 180

gcacagaagt ttcagggcag agtcaccgtg acctgggaca cctccatcag cacagcctac 240

atggaactgt ccagcctgag ctctgaggac acggccatat attactgtgc gagagaacat 300

ggcagtagct ggggcttctt tgactactgg ggccagggaa ccctggtcac cgtctcctca 360

<210> 290
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 290

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

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

Asn Ile Phe Trp Val Arg Gln Ala Thr Gly Gln Gly Leu Asp Trp Met
35 40 45

Gly Trp Met Asn Pro Phe Arg Asn Asn Ala Gly Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Val Thr Trp Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Ser Ser Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Ala Arg Glu His Gly Ser Ser Trp Gly Phe Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 291
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 291
ggatacacct tcattagtta caat 24

<210> 292
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 292

Gly Tyr Thr Phe Ile Ser Tyr Asn
1 5

<210> 293

<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 293
atgaacccct tcagaaataa cgca 24

<210> 294
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 294

Met Asn Pro Phe Arg Asn Asn Ala
1 5

<210> 295
<211> 39
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 295
gcgagagaac atggcagtag ctggggcttc tttgactac 39

<210> 296
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 296

Ala Arg Glu His Gly Ser Ser Trp Gly Phe Phe Asp Tyr
1 5 10

<210> 297

<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 297
gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc 60

ctctcctgca gggccagtca gagtgttagc agcagctact tagcctggta ccagcagaaa 120

cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca 180

gacaggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagactggag 240

cctgaagatt ttgcagtgta ttactgtcag cagtatggta gctcaccttg gacgttcggc 300

caagggacca aggtggaaat caaa 324

<210> 298
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 298

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro

85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 299
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 299
cagagtgtta gcagcagcta c 21

<210> 300
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 300

Gln Ser Val Ser Ser Ser Tyr
1 5

<210> 301
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 301
ggtgcatcc 9

<210> 302
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 302

Gly Ala Ser
1

<210> 303
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 303
cagcagtatg gtagctcacc ttggacg 27

<210> 304
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 304

Gln Gln Tyr Gly Ser Ser Pro Trp Thr
1 5

<210> 305
<211> 483
<212> DNA
<213> Artificial Sequence

<220>
<223> Bet v1

<400> 305
atgggtgtgt ttaattatga gactgagacc acctctgtta tcccagcagc tcgactgttc 60

aaggccttta tccttgatgg cgataacctc tttccaaagg ttgcacccca agccattagc 120

agtgttgaaa acattgaagg aaatggaggg cctggaacca ttaagaagat cagctttccc 180

gaaggcctcc ctttcaagta cgtgaaggac agagttgatg aggtggacca cacaaacttc 240

aaatacaatt acagcgtgat cgagggcggt cccataggcg acacattgga gaagatctcc 300

aacgagataa agatagtggc aacccctgat ggaggatcca tcttgaagat cagcaacaag 360

taccacacca aaggtgacca tgaggtgaag gcagagcagg ttaaggcaag taaagaaatg 420

ggcgagacac ttttgagggc cgttgagagc tacctcttgg cacactccga tgcctacaac 480

taa 483

<210> 306
<211> 160
<212> PRT
<213> Artificial Sequence

<220>
<223> Bet v1 (M1-N160 of accession number CAB02159)

<400> 306

Met Gly Val Phe Asn Tyr Glu Thr Glu Thr Thr Ser Val Ile Pro Ala
1 5 10 15

Ala Arg Leu Phe Lys Ala Phe Ile Leu Asp Gly Asp Asn Leu Phe Pro
20 25 30

Lys Val Ala Pro Gln Ala Ile Ser Ser Val Glu Asn Ile Glu Gly Asn
35 40 45

Gly Gly Pro Gly Thr Ile Lys Lys Ile Ser Phe Pro Glu Gly Leu Pro
50 55 60

Phe Lys Tyr Val Lys Asp Arg Val Asp Glu Val Asp His Thr Asn Phe
65 70 75 80

Lys Tyr Asn Tyr Ser Val Ile Glu Gly Gly Pro Ile Gly Asp Thr Leu
85 90 95

Glu Lys Ile Ser Asn Glu Ile Lys Ile Val Ala Thr Pro Asp Gly Gly
100 105 110

Ser Ile Leu Lys Ile Ser Asn Lys Tyr His Thr Lys Gly Asp His Glu
115 120 125

Val Lys Ala Glu Gln Val Lys Ala Ser Lys Glu Met Gly Glu Thr Leu

130 135 140

Leu Arg Ala Val Glu Ser Tyr Leu Leu Ala His Ser Asp Ala Tyr Asn
145 150 155 160

<210> 307
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> AA 23-43 of Bet v1

<400> 307

Phe Ile Leu Asp Gly Asp Asn Leu Phe Pro Lys Val Ala Pro Gln Ala
1 5 10 15

Ile Ser Ser Val Glu
20

<210> 308
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> AA 44-56 of Bet v1

<400> 308

Asn Ile Glu Gly Asn Gly Gly Pro Gly Thr Ile Lys Lys
1 5 10

<210> 309
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> AA 2-19 of Bet v1

<400> 309

Gly Val Phe Asn Tyr Glu Thr Glu Thr Thr Ser Val Ile Pro Ala Ala
1 5 10 15

Arg Leu

<210> 310
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> AA 57-70 of Bet v1

<400> 310

Ile Ser Phe Pro Glu Gly Leu Pro Phe Lys Tyr Val Lys Asp
1 5 10

<210> 311
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> AA 81-89 of Bet v1

<400> 311

Lys Tyr Asn Tyr Ser Val Ile Glu Gly
1 5

<210> 312
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Mutant Bet v 1-MMH w S85A (1-159: Bet v1 (G2-N160 of accession number CAB02159) with Myc-Myc hexahistidine tag

<400> 312

Gly Val Phe Asn Tyr Glu Thr Glu Thr Thr Ser Val Ile Pro Ala Ala
1 5 10 15

Arg Leu Phe Lys Ala Phe Ile Leu Asp Gly Asp Asn Leu Phe Pro Lys
20 25 30

Val Ala Pro Gln Ala Ile Ser Ser Val Glu Asn Ile Glu Gly Asn Gly
        35   40   45

Gly Pro Gly Thr Ile Lys Lys Ile Ser Phe Pro Glu Gly Leu Pro Phe
    50   55   60

Lys Tyr Val Lys Asp Arg Val Asp Glu Val Asp His Thr Asn Phe Lys
65   70   75   80

Tyr Asn Tyr Ala Val Ile Glu Gly Gly Pro Ile Gly Asp Thr Leu Glu
                85   90   95

Lys Ile Ser Asn Glu Ile Lys Ile Val Ala Thr Pro Asp Gly Gly Ser
            100   105   110

Ile Leu Lys Ile Ser Asn Lys Tyr His Thr Lys Gly Asp His Glu Val
        115   120   125

Lys Ala Glu Gln Val Lys Ala Ser Lys Glu Met Gly Glu Thr Leu Leu
    130   135   140

Arg Ala Val Glu Ser Tyr Leu Leu Ala His Ser Asp Ala Tyr Asn Glu
145   150   155   160

Gln Lys Leu Ile Ser Glu Glu Asp Leu Gly Gly Glu Gln Lys Leu Ile
                165   170   175

Ser Glu Glu Asp Leu His His His His His His
            180   185

<210> 313
<211> 413
<212> PRT
<213> Artificial Sequence

<220>
<223> hFceR1alpha-mFc

<400> 313

Val Pro Gln Lys Pro Lys Val Ser Leu Asn Pro Pro Trp Asn Arg Ile
1   5   10   15

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Phe Lys Gly Glu Asn Val Thr Leu Thr Cys Asn Gly Asn Asn Phe Phe
            20                  25                  30

Glu Val Ser Ser Thr Lys Trp Phe His Asn Gly Ser Leu Ser Glu Glu
        35                  40                  45

Thr Asn Ser Ser Leu Asn Ile Val Asn Ala Lys Phe Glu Asp Ser Gly
    50                  55                  60

Glu Tyr Lys Cys Gln His Gln Gln Val Asn Glu Ser Glu Pro Val Tyr
65                  70                  75                  80

Leu Glu Val Phe Ser Asp Trp Leu Leu Leu Gln Ala Ser Ala Glu Val
                85                  90                  95

Val Met Glu Gly Gln Pro Leu Phe Leu Arg Cys His Gly Trp Arg Asn
            100                 105                 110

Trp Asp Val Tyr Lys Val Ile Tyr Tyr Lys Asp Gly Glu Ala Leu Lys
        115                 120                 125

Tyr Trp Tyr Glu Asn His Asn Ile Ser Ile Thr Asn Ala Thr Val Glu
    130                 135                 140

Asp Ser Gly Thr Tyr Tyr Cys Thr Gly Lys Val Trp Gln Leu Asp Tyr
145                 150                 155                 160

Glu Ser Glu Pro Leu Asn Ile Thr Val Ile Lys Ala Pro Arg Glu Lys
                165                 170                 175

Tyr Trp Leu Gln Glu Pro Arg Gly Pro Thr Ile Lys Pro Cys Pro Pro
            180                 185                 190

Cys Lys Cys Pro Ala Pro Asn Leu Leu Gly Gly Pro Ser Val Phe Ile
        195                 200                 205

Phe Pro Pro Lys Ile Lys Asp Val Leu Met Ile Ser Leu Ser Pro Ile
    210                 215                 220
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Val Thr Cys Val Val Val Asp Val Ser Glu Asp Asp Pro Asp Val Gln
225                 230                 235                 240


Ile Ser Trp Phe Val Asn Asn Val Glu Val His Thr Ala Gln Thr Gln
                245                 250                 255


Thr His Arg Glu Asp Tyr Asn Ser Thr Leu Arg Val Val Ser Ala Leu
            260                 265                 270


Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys Glu Phe Lys Cys Lys
        275                 280                 285


Val Asn Asn Lys Asp Leu Pro Ala Pro Ile Glu Arg Thr Ile Ser Lys
    290                 295                 300


Pro Lys Gly Ser Val Arg Ala Pro Gln Val Tyr Val Leu Pro Pro Pro
305                 310                 315                 320


Glu Glu Glu Met Thr Lys Lys Gln Val Thr Leu Thr Cys Met Val Thr
                325                 330                 335


Asp Phe Met Pro Glu Asp Ile Tyr Val Glu Trp Thr Asn Asn Gly Lys
            340                 345                 350


Thr Glu Leu Asn Tyr Lys Asn Thr Glu Pro Val Leu Asp Ser Asp Gly
        355                 360                 365


Ser Tyr Phe Met Tyr Ser Lys Leu Arg Val Glu Lys Lys Asn Trp Val
    370                 375                 380


Glu Arg Asn Ser Tyr Ser Cys Ser Val Val His Glu Gly Leu His Asn
385                 390                 395                 400


His His Thr Thr Lys Ser Phe Ser Arg Thr Pro Gly Lys
                405                 410


<210>  314
<211>  160
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<212> PRT
<213> Artificial Sequence

<220>
<223> Bet v 1 amino acid sequence from Uniprot: P15494

<400> 314

Met Gly Val Phe Asn Tyr Glu Thr Glu Thr Thr Ser Val Ile Pro Ala
1 5 10 15

Ala Arg Leu Phe Lys Ala Phe Ile Leu Asp Gly Asp Asn Leu Phe Pro
20 25 30

Lys Val Ala Pro Gln Ala Ile Ser Ser Val Glu Asn Ile Glu Gly Asn
35 40 45

Gly Gly Pro Gly Thr Ile Lys Lys Ile Ser Phe Pro Glu Gly Phe Pro
50 55 60

Phe Lys Tyr Val Lys Asp Arg Val Asp Glu Val Asp His Thr Asn Phe
65 70 75 80

Lys Tyr Asn Tyr Ser Val Ile Glu Gly Gly Pro Ile Gly Asp Thr Leu
85 90 95

Glu Lys Ile Ser Asn Glu Ile Lys Ile Val Ala Thr Pro Asp Gly Gly
100 105 110

Ser Ile Leu Lys Ile Ser Asn Lys Tyr His Thr Lys Gly Asp His Glu
115 120 125

Val Lys Ala Glu Gln Val Lys Ala Ser Lys Glu Met Gly Glu Thr Leu
130 135 140

Leu Arg Ala Val Glu Ser Tyr Leu Leu Ala His Ser Asp Ala Tyr Asn
145 150 155 160

<210> 315
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> AA 81-96 of Bet v1

<400> 315

Lys Tyr Asn Tyr Ser Val Ile Glu Gly Gly Pro Ile Gly Asp Thr Leu
1   5   10   15

<210> 316
<211> 446
<212> PRT
<213> Artificial Sequence

<220>
<223> H4H17038P2 HC

<400> 316

Glu Val Gln Leu Val Glu Ser Gly Gly Asp Leu Val Gln Pro Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20   25   30

Glu Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ser Phe Ile Ser Asp Ser Ser Ser Asn Ile Tyr Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Lys Ser Leu Tyr
65   70   75   80

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

Ala Arg Glu Ala Ile Gly Ser Thr Ser Phe Asp Asn Trp Gly Gln Gly
            100   105   110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
        115   120   125

```
Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu
    130                 135                 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145                 150                 155                 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
            180                 185                 190

Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro
        195                 200                 205

Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro
    210                 215                 220

Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe
225                 230                 235                 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
                245                 250                 255

Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val
            260                 265                 270

Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
        275                 280                 285

Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val
    290                 295                 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305                 310                 315                 320

Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser
                325                 330                 335
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Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
            340                 345                 350


Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
        355                 360                 365


Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
    370                 375                 380


Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385                 390                 395                 400


Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp
                405                 410                 415


Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
            420                 425                 430


Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
        435                 440                 445


<210>  317
<211>  214
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  H4H17038P2 LC

<400>  317

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1               5                   10                  15


Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Arg Leu Ile
        35                  40                  45


Tyr Ser Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60
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```
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65                  70                  75                  80

Glu Asp Phe Ala Ile Tyr Tyr Cys His Gln Tyr Asn Asn Trp Pro Leu
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210


<210>  318
<211>  446
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  H4H16987P HC

<400>  318
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Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                  10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Ser Ser Asn
            20                  25                  30

Ser Met Ser Trp Val Arg Gln Ala Pro Gly Glu Gly Leu Glu Trp Val
        35                  40                  45

Ser Val Ile Phe Ser Gly Gly Ile Thr Tyr Tyr Ser Asp Ser Val Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Arg His Asn Ser Lys Asn Thr Leu Tyr Leu
65                  70                  75                  80

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

Arg His Ser Asn Trp Asn Phe Asp Ala Phe Asp Ile Trp Gly Gln Gly
            100                 105                 110

Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
        115                 120                 125

Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu
    130                 135                 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145                 150                 155                 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
            180                 185                 190

Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro
        195                 200                 205
```

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Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro
    210                 215                 220

Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe
225                 230                 235                 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
                245                 250                 255

Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val
            260                 265                 270

Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
        275                 280                 285

Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val
    290                 295                 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305                 310                 315                 320

Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser
                325                 330                 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
            340                 345                 350

Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
        355                 360                 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
    370                 375                 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385                 390                 395                 400

Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp
                405                 410                 415
```

Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
435 440 445

<210> 319
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> H4H16987P LC

<400> 319

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Phe Asp Thr Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Asn Leu Leu Ile
35 40 45

Tyr Ala Thr Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Gly Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Ile Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

```
Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160


Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175


Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190


Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205


Phe Asn Arg Gly Glu Cys
    210


<210>  320
<211>  443
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  H4H16992P HC

<400>  320

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1               5                   10                  15


Thr Leu Ser Leu Thr Cys Ser Val Ser Gly Gly Ser Ile Thr Asn Tyr
            20                  25                  30


Phe Trp Thr Trp Ile Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45


Gly Tyr Ile Tyr Tyr Ser Gly Gly Thr Asn Tyr Asn Pro Ser Leu Lys
    50                  55                  60


Ser Arg Val Thr Ile Ser Ile Asp Thr Ser Lys Asn Gln Phe Ser Leu
65                  70                  75                  80
```

```
Asn Met Asn Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95

Gly Ser Tyr Tyr Tyr Gly Val Asp Val Trp Gly Gln Gly Thr Thr Val
            100                 105                 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
        115                 120                 125

Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu
    130                 135                 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145                 150                 155                 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
                165                 170                 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
            180                 185                 190

Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr
        195                 200                 205

Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro
    210                 215                 220

Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
225                 230                 235                 240

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
                245                 250                 255

Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn
            260                 265                 270

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
        275                 280                 285
```

```
Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
    290                 295                 300

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
305                 310                 315                 320

Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys
                325                 330                 335

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu
            340                 345                 350

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
        355                 360                 365

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
    370                 375                 380

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
385                 390                 395                 400

Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly
                405                 410                 415

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
            420                 425                 430

Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
        435                 440
```

<210> 321
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> H4H16992P LC

<400> 321

```
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15
```

```
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Lys Ser Phe
            20                  25                  30

Leu Ala Trp Tyr Arg Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45

Tyr Asp Ala Ser Asn Arg Pro Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Leu Glu Ser
65                  70                  75                  80

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Arg Asn Asn Trp Pro Phe
                85                  90                  95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210
```

<210> 322
<211> 447
<212> PRT
<213> Artificial Sequence

<220>
<223> H4H17082P2 HC

<400> 322

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


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


Asn Ile Phe Trp Val Arg Gln Ala Thr Gly Gln Gly Leu Asp Trp Met
        35                  40                  45


Gly Trp Met Asn Pro Phe Arg Asn Asn Ala Gly Tyr Ala Gln Lys Phe
    50                  55                  60


Gln Gly Arg Val Thr Val Thr Trp Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80


Met Glu Leu Ser Ser Leu Ser Ser Glu Asp Thr Ala Ile Tyr Tyr Cys
                85                  90                  95


Ala Arg Glu His Gly Ser Ser Trp Gly Phe Phe Asp Tyr Trp Gly Gln
            100                 105                 110


Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125


Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
    130                 135                 140


Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160
```

```
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
    210                 215                 220

Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val
225                 230                 235                 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                245                 250                 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
            260                 265                 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        275                 280                 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
    290                 295                 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
                325                 330                 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
            340                 345                 350

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
        355                 360                 365
```

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
435 440 445

<210> 323
<211> 215
<212> PRT
<213> Artificial Sequence

<220>
<223> H4H17082P2 LC

<400> 323

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
85 90 95

```
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
            100                 105                 110

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
        115                 120                 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
    130                 135                 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145                 150                 155                 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
                165                 170                 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
            180                 185                 190

Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
        195                 200                 205

Ser Phe Asn Arg Gly Glu Cys
    210                 215
```