offered as an alternative strategy to provide potent, antigen-specific molecules, but dosing with such conjugates or chimeras can be limited by excessive and/or non-specific toxicity due to the toxin moiety of such preparations. Toxic effects may include supraphysiological elevation of liver enzymes and vascular leak syndrome, and other undesired effects. In addition, immunotoxins are themselves highly immunogenic upon administration to a host, and host antibodies generated against the immunotoxin limit potential usefulness for repeated therapeutic treatments of an individual.

[0026] Other engineered fusion proteins, termed small, modular immunopharmaceutical (SMIP™) products, are described in co-owned US Patent Publications 2003/133939., 2003/0118592, and 2005/0136049, and co-owned International Patent Publications WO02/056910, WO2005/037989., and WO2005/017148, which are all incorporated by reference herein. SMIP products are novel binding domain-immunoglobulin fusion proteins that feature a binding domain for a cognate structure such as an antigen, a counterreceptor or the like; an IgG1, IGA or IgE hinge region polypeptide or a mutant IgG1 hinge region polypeptide having either zero, one or two cysteine residues; and immunoglobulin CH2 and CH3 domains. SMIP products are capable of ADCC and/or CDC.

[0027] Although there has been extensive research carried out on antibody-based therapies, there remains a need in the art for improved methods to treat diseases associated with aberrant B-cell activity. The methods of the present invention described and claimed herein provide such improved methods as well as other advantages.

SUMMARY ~~OF THE INVENTION~~

[0027a] In a first aspect, the present invention is directed to a humanized CD37-specific binding protein for use in treating a B-cell cancer or an autoimmune disease, wherein the humanized CD37-specific binding protein comprises:

(a) human light chain framework regions, a light chain CDR1 comprising an amino acid sequence of SEQ ID NO:61, a light chain CDR2 comprising an amino acid sequence of SEQ ID NO:64, and a light chain CDR3 comprising an amino acid sequence of SEQ ID NO:66; and

(b) human heavy chain framework regions, a heavy chain CDR1 comprising an amino acid sequence of SEQ ID NO:63, a heavy chain CDR2 comprising an amino acid sequence of SEQ ID NO:65, and a heavy chain CDR3 comprising an amino acid sequence of SEQ ID NO: 67 or 68

characterized in that the humanized CD37-specific binding protein is to be used in combination with a CD20-specific binding protein.

[0027b] In a second aspect, the present invention is directed to a CD20-specific binding protein for use in treating a B-cell cancer or an autoimmune disease characterized in that the CD20-specific binding protein is to be used in combination with a humanized CD37-specific binding protein for use in treating a B-cell cancer or an autoimmune disease, wherein the humanized CD37-specific binding protein comprises:

(a) human light chain framework regions, a light chain CDR1 comprising an amino acid sequence of SEQ ID NO:61, a light chain CDR2 comprising an amino acid sequence of SEQ ID NO:64, and a light chain CDR3 comprising an amino acid sequence of SEQ ID NO:66; and

(b) human heavy chain framework regions, a heavy chain CDR1 comprising an amino acid sequence of SEQ ID NO:63, a heavy chain CDR2 comprising an amino acid sequence of SEQ ID NO:65, and a heavy chain CDR3 comprising an amino acid sequence of SEQ ID NO: 67 or 68.

[0027c] In a third aspect, the present invention is directed to an article of manufacture comprising a CD20-specific binding protein and a humanized CD37-specific binding protein for use in treating a B-cell cancer or an autoimmune disease, wherein the humanized CD37-specific binding protein comprises:

(a) human light chain framework regions, a light chain CDR1 comprising an amino acid sequence of SEQ ID NO:61, a light chain CDR2 comprising an amino acid sequence of SEQ ID NO:64, and a light chain CDR3 comprising an amino acid sequence of SEQ ID NO:66; and

(b) human heavy chain framework regions, a heavy chain CDR1 comprising an amino acid sequence of SEQ ID NO:63, a heavy chain CDR2 comprising an amino acid sequence of SEQ ID NO:65, and a heavy chain CDR3 comprising an amino acid sequence of SEQ ID NO: 67 or 68.

[0028] Further described are~~The present invention provides~~ methods for reducing B-cells using CD37-specific binding molecules. In some methods described herein~~of the invention~~, use of combinations of CD37-specific binding molecules (one or more CD37-specific binding molecules) and CD20-specific binding molecules (one or more CD20-

specific binding molecules) results in increased B-cell reduction. In some of these methods, the combinations are synergistic. In a related example, described isaspect, the invention provides a method of treating an individual having, or suspected of having, a disease associated with aberrant B-cell activity.

[0029] Also described areThe present invention also provides humanized CD37-specific binding molecules (e.g., humanized TRU-016 constructs) and methods for reducing B-cells using these molecules. In some examplesembodiments of the methods of the invention, uses of combinations of humanized TRU-016 constructs with one or more CD20-specific binding molecules is contemplated. In another example,aspect, the invention provides methods are described forof treating individuals having, or suspected of having, a disease associated with aberrant B-cell activity. Related examplesaspects of the invention are drawn to methods of preventing any such disease and methods of ameliorating a symptom associated with such a disease comprising administering a dose of a humanized CD37-specific binding molecule effective to treat or prevent such disease, or to ameliorate a symptom of such disease.

[0030] "Aberrant B-cell activity" refers to B-cell activity that deviates from the normal, proper, or expected course. For example, aberrant B-cell activity may include inappropriate proliferation of cells whose DNA or other cellular components have become damaged or defective. Aberrant B-cell activity may include cell proliferation whose characteristics are associated with a disease caused by, mediated by, or resulting in inappropriately high levels of cell division, inappropriately low levels of apoptosis, or both. Such diseases may be characterized, for example, by single or multiple local abnormal proliferations of cells, groups of cells or tissue(s), whether cancerous or non-cancerous, benign or malignant. Aberrant B-cell activity may also include aberrant antibody production, such as production of autoantibodies, or overproduction of antibodies typically desirable when produced at normal levels. It is contemplated that aberrant B-cell activity may occur in certain subpopulations of B-cells and not in other subpopulations. Aberrant B-cell activity may also include inappropriate stimulation of T-cells, such as by

inappropriate B-cell antigen presentation to T-cells or by other pathways involving B-cells.

[0031] "Treatment" or "treating" refers to either a therapeutic treatment or prophylactic/preventative treatment. A therapeutic treatment may improve at least one symptom of disease in an individual receiving treatment or may delay worsening of a progressive disease in an individual, or prevent onset of additional associated diseases.

[0032] A "therapeutically effective dose" or "effective dose" of a CD20-specific binding molecule refers to that amount of the compound sufficient to result in amelioration of one or more symptoms of the disease being treated. When applied to an individual active ingredient, administered alone, a therapeutically effective dose refers to that ingredient alone. When applied to a combination, a therapeutically effective dose refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered serially or simultaneously. Examples described herein~~The invention~~ specifically contemplates that one or more specific binding molecules may be administered according to methods described herein~~of the invention~~, each in an effective dose.

[0033] "An individual having, or suspected of having, a disease associated with aberrant B-cell activity" is an individual in whom a disease or a symptom of a disorder may be caused by aberrant B-cell activity, may be exacerbated by aberrant B-cell activity, or may be relieved by regulation of B-cell activity. Examples of such diseases are a B-cell cancer (for example, B-cell lymphoma, a B-cell leukemia or a B-cell myeloma), a disease characterized by autoantibody production or a disease characterized by inappropriate T-cell stimulation caused by inappropriate B-cell antigen presentation to T-cells or caused by other pathways involving B-cells.

[0034] In one exemplary aspect, an individual treated by methods described herein~~of the invention~~ demonstrates a response to treatment that is better than, or improved relative to, the response to treatment with rituximab. A response which is improved over treatment with rituximab refers to a clinical response wherein treatment by a method as described herein~~of the invention~~ results in a clinical response in a patient that is better than a clinical response in a patient receiving

rituximab therapy, such as rituximab. An improved response is assessed by comparison of clinical criteria well-known in the art and described herein. Exemplary criteria include, but are not limited to, duration of B cell depletion, reduction in B cell numbers overall, reduction in B cell numbers in a biological sample, reduction in tumor size, reduction in the number of tumors existing and/or appearing after treatment, and improved overall response as assessed by patients themselves and physicians, e.g., using an International Prognostic Index. The improvement may be in one or more than one of the clinical criteria. An improved response with the method described herein~~of the invention~~ may be due to an inadequate response to previous or current treatment with rituximab, for example, because of toxicity and/or inadequate efficacy of the rituximab treatment.

[0035] B-cell cancers include B-cell lymphomas [such as various forms of Hodgkin's disease, non-Hodgkins lymphoma (NHL) or central nervous system lymphomas], leukemias [such as acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), Hairy cell leukemia and chronic myoblastic leukemia] and myelomas (such as multiple myeloma). Additional B cell cancers include small lymphocytic lymphoma, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, splenic marginal zone lymphoma, plasma cell myeloma, solitary plasmacytoma of bone, extraosseous plasmacytoma, extra-nodal marginal zone B-cell lymphoma of mucosa-associated (MALT) lymphoid tissue, nodal marginal zone B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, diffuse large B-cell lymphoma, mediastinal (thymic) large B-cell lymphoma, intravascular large B-cell lymphoma, primary effusion lymphoma, Burkitt lymphoma/leukemia, B-cell proliferations of uncertain malignant potential, lymphomatoid granulomatosis, and post-transplant lymphoproliferative disorder.

[0036] Disorders characterized by autoantibody production are often considered autoimmune diseases. Autoimmune diseases include, but are not limited to: arthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, polychondritis, psoriatic arthritis, psoriasis, dermatitis, polymyositis/dermatomyositis, inclusion body myositis, inflammatory myositis,

[0049] IIM associated factors, including muscle-associated enzymes and autoantibodies include, but are not limited to, creatine kinase (CK), lactate dehydrogenase, aldolase, C-reactive protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and antinuclear autoantibody (ANA), myositis-specific antibodies (MSA), and antibody to extractable nuclear antigens.

[0050] A "binding molecule" as described hereinaccording to the invention can be, for example, a protein (a "protein" may be polypeptide or peptide), nucleic acid, carbohydrate, lipid, or small molecule compound that binds to a target. A type of proteinaceous binding molecule contemplated hereinby the invention is an antibody or an antibody fragment that retains binding activity. A binding molecule may be modified according to methods standard in the art to improve its binding affinity, diminish its immunogenicity, alter its effector functions and/or improve its availability in the body of an individual. Such modifications may include, for example, amino acid sequence modifications or expression as a fusion protein. Such fusion proteins are also binding molecules according to the invention. An exemplary binding molecule of the invention is a small modular immunopharmaceutical (SMIP™).

[0051] A binding molecule that is "specific" for a target binds to that target with a greater affinity than any other target. For example, a CD37-specific binding molecule binds to CD37 with a greater affinity than to any other target and a CD20-specific binding molecule binds to CD20 with a greater affinity than to any other target. Binding molecules as described hereinof the invention may have affinities for their targets of a Ka of greater than or equal to about 10^4 M^{-1}, preferably of greater than or equal to about 10^5 M^{-1}, more preferably of greater than or equal to about 10^6 M^{-1} and still more preferably of greater than or equal to about 10^7 M^{-1}. Affinities of even greater than about 10^7 M^{-1} are still more preferred, such as affinities equal to or greater than about 10^7 M^{-1}, about 10^8 M^{-1}, and about 10^9 M^{-1}, and about 10^{10} M^{-1}. Affinities of binding molecules as described hereinaccording to the present invention can be readily determined using conventional techniques, for example those described by Scatchard et al., Ann. N.Y. Acad. Sci. 51:660 (1949).

[0052] Certain CD37-specific binding molecules contemplated by the invention have affinities for CD37 of about 0.5 to about 10nM. Certain CD20-specific binding molecules contemplated by the invention have affinities for CD20 of about 1 to about 30 nM.

[0053] Another characteristic of certain CD37-binding molecules and CD20-binding molecules contemplated hereinby the invention is they exhibit a half life in circulation of about 7 to about 30 days.

[0054] CD37-specific antibodies that characterized the CD37 antigen in the Thrid HLDA Workshop were HD28, G28-1, HH1, BI14, WR17 and F93G6. See, Ling and MacLennan, pp. 302-335 in Leucocyte Typing III. White Cell Differentiation Antigens, Oxford University Press (1987). Other CD37-specific antibodies that have been described include RFB-7, Y29/55, MB-1, M-B371, M-B372 and IPO-24. See, Moldenhaurer, J. Biol., Regul. Homeost. Agents, 14: 281-283 (2000) which states that all these antibodies recognize only one CD37 epitope. Schwartz-Albiez et al., 14: 905-914 (1988) indicates that the epitope is situated in the carbohydrate moiety of CD37. Another CD37-specific antibody is S-B3 (Biosys).

[0055] Patents and patent publications describing CD20 antibodies include U.S. Pat. Nos. 5,776,456, 5,736,137, 6,399,061, and 5,843,439, as well as US patent application Nos. US 2002/0197255A1 and US 2003/0021781A1 (Anderson et al.); U.S. Pat. No. 6,455,043B1 and WO00/09160 (Grillo-Lopez, A.); WO00/27428 (Grillo-Lopez and White); WO00/27433 (Grillo-Lopez and Leonard); WO00/44788 (Braslawsky et al.); WO01/10462 (Rastetter, W.); WO01/10461 (Rastetter and White); WO01/10460 (White and Grillo-Lopez); US appln No. US2002/0006404 and WO02/04021 (Hanna and Hariharan); US appln No. US2002/0012665 A1 and WO01/74388 (Hanna, N.); US appln No. US2002/0009444A1, and WO01/80884 (Grillo-Lopez, A.); WO01/97858 (White, C.); US appln No. US2002/0128488A1 and WO02/34790 (Reff, M.);WO02/060955 (Braslawsky et al.);WO02/096948 (Braslawsky et al.);WO02/079255 (Reff and Davies); U.S. Pat. No. 6,171,586B1, and WO98/56418 (Lam et al.); WO98/58964 (Raju, S.); WO99/22764 (Raju, S.);WO99/51642, U.S. Pat. No. 6,194,551B1, U.S. Pat. No. 6,242,195B1,

U.S. Pat. No. 6,528,624B1 and U.S. Pat. No. 6,538,124 (Idusogie et al.); WO00/42072 (Presta, L.); WO00/67796 (Curd et al.); WO01/03734 (Grillo-Lopez et al.); US appln No. US 2002/0004587A1 and WO01/77342 (Miller and Presta); US appln No. US2002/0197256 (Grewal, I.); U.S. Pat. Nos. 6,090,365B1, 6,287,537B1, 6,015,542, 5,843,398, and 5,595,721, (Kaminski et al.); U.S. Pat. Nos. 5,500,362, 5,677,180, 5,721,108, and 6,120,767 (Robinson et al.); U.S. Pat No. 6,410,391B1 (Raubitschek et al.); U.S. Pat. No. 6,224,866B1 and WO00/20864 (Barbera-Guillem, E.); WO01/13945 (Barbera-Guillem, E.); WO00/67795 (Goldenberg); WO00/74718 (Goldenberg and Hansen); WO00/76542 (Golay et al.);WO01/72333 (Wolin and. Rosenblatt); U.S. Pat. No. 6,368,596B1 (Ghetie et al.); US Appln No. US2002/0041847A1, (Goldenberg, D.); US Appln no. US2003/0026801A1 (Weiner and Hartmann); WO02/102312 (Engleman, E.), each of which is expressly incorporated herein by reference. See, also, U.S. Pat. No. 5,849,898 and EP appln No. 330,191 (Seed et al.); U.S. Pat. No. 4,861,579 and EP332,865A2 (Meyer and Weiss); and WO95/03770 (Bhat et al.).

[0056] Rituximab has been approved for human clinical use as Rituxan®. Rituxan® is considered to be a CD20-specific binding molecule as defined herein~~of the invention~~.

[0057] Small, modular immunopharmaceuticals (SMIPs) are considered to be one type of binding molecules described herein~~of the invention~~. Methods for making SMIPs have been described previously in co-owned U.S. application no. 10/627,556 and US Patent Publ. 20030133939, 20030118592, and 20050136049, which are incorporated herein by reference in their entirety. SMIPs are novel binding domain-immunoglobulin fusion proteins that generally feature a binding domain for a cognate structure such as an antigen, a counterreceptor or the like, an IgG1, IGA or IgE hinge region polypeptide or a mutant IgG1 hinge region polypeptide having either zero, one or two cysteine residues, and immunoglobulin CH2 and CH3 domains. In one example~~embodiment~~, the binding domain molecule has one or two cysteine (Cys) residues in the hinge region. In a related example~~embodiment~~, when the binding domain molecule comprises two

Cys residues, the first Cys, which is involved in binding between the heavy chain and light chain, is not deleted or substituted with an amino acid.

[0058] The binding domain of molecules useful in methods described hereinof the invention are contemplated as having one or more binding regions, such as variable light chain and variable heavy chain binding regions derived from one or more immunoglobulin superfamily members, such as an immunoglobulin. These regions, moreover, are typically separated by linker peptides, which may be any linker peptide known in the art to be compatible with domain or region joinder in a binding molecule. Exemplary linkers are linkers based on the Gly_4Ser linker motif, such as $(Gly_4Ser)_n$, where n=1-5. The molecules for use in the methods described hereinof the invention also contain sufficient amino acid sequence derived from a constant region of an immunoglobulin to provide an effector function, preferably ADCC and/or CDC. Thus, the molecules will have a sequence derived from a CH2 domain of an immunoglobulin or CH2 and CH3 domains derived from one or more immunoglobulins. SMIPs are capable of ADCC and/or CDC but are compromised in their ability to form disulfide-linked multimers.

[0059] Described herein areThe invention includes humanized CD37-specific SMIP polypeptides that exhibit at least 80 percent identity to the polypeptide set forth in SEQ ID NO: 2, wherein the humanized CD37-specific SMIP polypeptide binds CD37. In one exampleaspect, the humanized CD37-specific SMIP polypeptides comprise any amino acid sequence selected from the group consisting of SEQ ID NOS: 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 80, 82, 84, 86, and 88. In another exampleaspect, the humanized CD37-specific SMIP polypeptides comprise at least one amino acid modification in a complementarity-determining region (CDR) selected from the group consisting of: light chain CDR1, heavy chain CDR1, light chain CDR2, heavy chain CDR2, light chain CDR3, and heavy chain CDR3.

[0060] In one exampleembodiment, the invention includes a humanized CD37-specific SMIP polypeptide is described, wherein CDR1 of the light chain comprises the amino acid sequence of SEQ ID NO: 61 (RASENVYSYLA). Also described isThe invention also includes a humanized CD37-specific SMIP polypeptide, wherein CDR1 of

the light chain comprises the amino acid sequence of SEQ ID NO: 62 (RTSENVYSYLA). Also described isThe invention further includes a humanized CD37-specific SMIP polypeptide, wherein CDR1 of the heavy chain comprises the amino acid sequence of SEQ ID NO: 63 (-GYNMN).

[0061] In another example,embodiment, the invention includes a humanized CD37-specific SMIP polypeptide is described, wherein CDR2 of the light chain comprises the amino acid sequence of SEQ ID NO: 64 (FAKTLAE). AThe invention also includesdescribed is a humanized CD37-specific SMIP polypeptide, wherein CDR2 of the heavy chain comprises the amino acid sequence of SEQ ID NO: 65 (NIDPYYGGTTYNRKFKG).

[0062] In a further example,embodiment, the invention includes a humanized CD37-specific SMIP polypeptide is described, wherein CDR3 of the light chain comprises the amino acid sequence of SEQ ID NO: 66 (QHHSDNPWT). Described is alsoThe invention further includes a humanized CD37-specific SMIP polypeptide, wherein CDR3 of the heavy chain comprises the amino acid sequence of SEQ ID NO: 67 (SVGPFDY). Also described isThe invention further includes a humanized CD37-specific SMIP polypeptide, wherein CDR3 of the heavy chain comprises the amino acid sequence of SEQ ID NO: 68 (SVGPFDS). Also described isThe invention also includes a humanized CD37-specific SMIP polypeptide, wherein CDR3 of the heavy chain comprises the amino acid sequence of SEQ ID NO: 69 (SVGPMDY).

[0063] Further described isIn another aspect, the invention includes a humanized CD37-specific SMIP polypeptide comprising at least one, at least two, or at least three sequence(s) of the light chain CDR amino acid sequences selected from the group consisting of SEQ ID NOS: 61, 62, 64, and 66. In yet another example,embodiment, the invention includes a humanized CD37-specific SMIP polypeptide is described that is comprising a light chain CDR1 amino acid sequence of SEQ ID NOS: 61 or 62, or a variant thereof in which one or two amino acids of SEQ ID NOS: 61 or 62 has been changed; a light chain CDR2 amino acid sequence of SEQ ID NO: 64, or a variant thereof in which one or two amino acids of SEQ ID NO: 64 has been changed; and a light chain CDR3 amino acid sequence of SEQ ID NO: 66, or a variant thereof in which one or two amino acids of SEQ ID NO: 66 has been changed.

[0064] In still another example,~~aspect, the invention includes~~ a humanized CD37-specific SMIP polypeptide is described that is comprising at least one, at least two, or at least three of the heavy chain CDR amino acid sequences selected from the group consisting of SEQ ID NOS: 63, 65, and 67-69. In a further example~~embodiment~~, ~~the invention includes~~ a humanized CD37-specific SMIP polypeptide is described that is comprising a heavy chain CDR1 amino acid sequence of SEQ ID NO: 63, or a variant thereof in which one or two amino acids of SEQ ID NO: 63 has been changed; a heavy chain CDR2 amino acid sequence of SEQ ID NO: 65, or a variant thereof in which one or two amino acids of SEQ ID NO: 65 has been changed; and a heavy chain CDR3 amino acid sequence selected from the group consisting of SEQ ID NOS: 67-69, or a variant thereof in which one or two amino acids of any one of SEQ ID NOS: 67-69 has been changed.

[0065] Also described are~~The invention also includes~~ humanized CD37-specific SMIP polypeptides comprising at least one amino acid modification in a framework region (FR) selected from the group consisting of: light chain FR1, heavy chain FR1, light chain FR2, heavy chain FR2, light chain FR3, heavy chain FR3, light chain FR4, and heavy chain FR4. In one example, described is~~embodiment, the invention includes~~ a humanized CD37-specific SMIP polypeptide, wherein the first framework region (FR1) of the light chain comprises the amino acid sequence of SEQ ID NO: 70 (EIVLTQSPATLSLSPGERATLSC). In another example,~~embodiment, the invention includes~~ a humanized CD37-specific SMIP polypeptide is described, wherein FR1 of the heavy chain comprises the amino acid sequence of SEQ ID NO: 71 (EVQLVQSGAEVKKPGESLKISCKGSGYSFT). In still another example,~~embodiment, the invention includes~~ a humanized CD37-specific SMIP polypeptide is described, wherein FR2 of the light chain comprises the amino acid sequence of SEQ ID NO: 72 (WYQQKPGQAPRLLIY). In a further example,~~embodiment, the invention includes~~ a humanized CD37-specific SMIP polypeptide is described, wherein FR2 of the heavy chain comprises the amino acid sequence of SEQ ID NO: 73 (WVRQMPGKGLEWMG). In yet another example,~~embodiment, the invention includes~~ a humanized CD37-specific SMIP polypeptide is described, wherein FR3 of the light chain comprises the amino acid sequence of SEQ ID NO: 74 (GIPARFSGSGSGTDFTLTISSLEPEDFAVYYC). In yet another example,~~embodiment, the invention includes~~ a humanized CD37-specific

SMIP polypeptide is described, wherein FR3 of the heavy chain comprises the amino acid sequence of SEQ ID NO: 75 (QVTISADKSISTAYLQWSSLKASDTAMYYCAR). In yet another example~~embodiment~~, ~~the invention includes~~ a humanized CD37-specific SMIP polypeptide is described, wherein FR4 of the light chain comprises the amino acid sequence of SEQ ID NO: 76 (FGQGTKVEIK). In yet another example~~embodiment~~, ~~the invention includes~~ a humanized CD37-specific SMIP polypeptide is described, wherein FR4 of the heavy chain comprises the amino acid sequence of SEQ ID NO: 77 (WGQGTLVTVSS). In yet another example~~embodiment~~, ~~the invention includes~~ a humanized CD37-specific SMIP polypeptide is described, wherein FR4 of the heavy chain comprises the amino acid sequence of SEQ ID NO: 78 (WGRGTLVTVSS).

[0066] Further described are~~The invention further includes~~ humanized CD37-specific SMIP polypeptides comprising at least one, at least two, or at least three sequence(s) of the light chain FR amino acid sequences selected from the group consisting of SEQ ID NOS: 70, 72, 74, and 76. In one example~~embodiment~~, ~~the invention includes~~ a humanized CD37-specific SMIP polypeptide is described that is comprising a light chain FR1 amino acid sequence of SEQ ID NO: 70, or a variant thereof in which one or two amino acids of SEQ ID NO: 70 has been changed; a light chain FR2 amino acid sequence of SEQ ID NO: 72, or a variant thereof in which one or two amino acids of SEQ ID NO: 72 has been changed; a light chain FR3 amino acid sequence of SEQ ID NO: 74, or a variant thereof in which one or two amino acids of SEQ ID NO: 74 has been changed; and a light chain FR4 amino acid sequence of SEQ ID NO: 76, or a variant thereof in which one or two amino acids of SEQ ID NO: 76 has been changed.

[0067] In addition, ~~the invention includes~~ humanized CD37-specific SMIP polypeptides are described that are comprising at least one, at least two, or at least three sequence(s) of the heavy chain FR amino acid sequences selected from the group consisting of SEQ ID NOS: 71, 73, 75, 77, and 78. In one example~~embodiment~~, ~~the invention includes~~ a humanized CD37-specific SMIP polypeptide is described that is comprising a heavy chain FR1 amino acid sequence of SEQ ID NO: 71, or a variant thereof in which one or two amino acids of SEQ ID NO: 71 has been changed; a heavy chain FR2 amino acid sequence of SEQ ID NO: 73, or a

variant thereof in which one or two amino acids of SEQ ID NO: 73 has been changed; a heavy chain FR3 amino acid sequence of SEQ ID NO: 75, or a variant thereof in which one or two amino acids of SEQ ID NO: 75 has been changed; and a heavy chain FR4 amino acid sequence of SEQ ID NOS: 77 or 78, or a variant thereof in which one or two amino acids of SEQ ID NOS: 77 or 78 has been changed.

[0068] Further disclosed is~~The invention also includes~~ an isolated nucleic acid molecule comprising a nucleotide sequence encoding a humanized CD37-specific SMIP polypeptide that exhibits at least 80 percent identity to the polypeptide set forth in SEQ ID NO: 2, wherein the humanized CD37-specific SMIP polypeptide binds CD37. Such an isolated nucleic acid molecule may comprise a nucleotide sequence selected from the group consisting of: SEQ ID NOS: 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 79, 81, 83, 85, and 87. In one example~~embodiment~~, ~~the invention includes~~ vectors are described that comprise these nucleic acid molecules and host cells that comprise the vectors.

[0069] Also described are~~The invention also includes~~ processes of producing the polypeptides described herein, comprising culturing the host cells under suitable conditions to express the polypeptides, and optionally isolating the polypeptides from the culture.

[0070] In yet another example~~aspect~~, ~~the invention includes~~ compositions are described comprising the humanized CD37-specific SMIP polypeptides described herein~~of the invention~~ and a pharmaceutically acceptable carrier.

[0071] Also described is~~The invention further includes~~ using the CD37-specific SMIP or CD37-specific binding molecules described herein in any of the methods described herein~~of the invention~~. Such methods include the use of any of the CD37-specific SMIP or CD37-specific binding molecule comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 80, 82, 84, 86, and 88.

[0072] In yet another exampleaspect, the invention includes kits for reducing B-cells are described comprising the compositions of the invention; and protocols for using the kits to reduce B cells. Such kits may further comprise one or more CD20-specific binding molecule(s). The disclosureinvention contemplates that such a CD20-specific binding molecule is TRU-015.

[0073] Also described areThe invention also includes humanized CD37-specific SMIP polypeptides comprising a CDR1, a CDR2, and a CDR3, that exhibits at least 80 percent identity to the polypeptide set forth in SEQ ID NO: 2. Such CD37-specific SMIP polypeptides may further comprise a human framework domain separating each of CDR1, CDR2, and CDR3.

[0074] In another exampleaspect, the invention includes a humanized CD37-specific SMIP polypeptide is described that exhibits at least 80 percent identity to the polypeptide set forth in SEQ ID NO: 2, wherein the humanized CD37-specific SMIP polypeptide binds CD37 and comprises a hinge region polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 90, 92, 94, 96, 98, 100, 102, 104, 106, 108 110, 112, 114, 115, 116, 118, 120, 122, 124, 126 and 127.

[0075] The disclosureinvention also contemplates a humanized CD37-specific SMIP polypeptide that exhibits at least 80 percent identity to the polypeptide set forth in SEQ ID NO: 2, wherein the humanized CD37-specific SMIP polypeptide binds CD37 and comprises a linker comprising (Gly4Ser)n, wherein n is 1, 2, 3, 4, 5, or 6.

[0076] In still a further example,aspect, the invention includes a humanized CD37-specific SMIP polypeptide is described, wherein CDR1 of the light chain comprises the amino acid sequence selected from the group consisting of SEQ ID NOS: 128 (RTSQNVYSYLA), 129 (RTSESVYSYLA), 130 (RASQSVYSYLA), 131 (RASQSVSSYLA) and 132 (RASQSVSYYLA). In another exampleembodiment, the invention includes a humanized CD37-specific SMIP polypeptide is described, wherein CDR1 of the heavy chain comprises the amino acid sequence selected from the group consisting of SEQ ID NOS: 133 (SYMNM) and 134 (SYWIG). In a further exampleembodiment, the invention includes a humanized CD37-specific SMIP polypeptide is described, wherein CDR2 of the light chain comprises the amino acid

sequence selected from the group consisting of SEQ ID NOS: 135 (AASSLQS), 136 (GASTRAT) and 137 (DASNRAT). In still another exampleembodiment, ~~the invention includes~~ a humanized CD37-specific SMIP polypeptide is described, wherein CDR2 of the heavy chain comprises the amino acid sequence selected from the group consisting of SEQ ID NOS: 138 (IIYPGDSDTRYSPSFQG) and 139 (RIDPSDSYTNYSPSFQG).

[0077] Also described is~~The invention also includes~~ a humanized CD37-specific SMIP polypeptide, wherein CDR3 of the light chain comprises the amino acid sequence of SEQ ID NO: 220 (QHHSDNPWT). In another exampleembodiment, ~~the invention includes~~ a humanized CD37-specific SMIP polypeptide is described, wherein CDR3 of the heavy chain comprises the amino acid sequence selected from the group consisting of SEQ ID NOS: 211 (SVGPMDY), 212 (SVGPFDY), 213 (SVGPMDV), 214 (SVGPFDS), 215 (SVGPFDP), 216 (SVGPFQH), 217 (SVGPFDV), 218 (SVGPFDI) and 219 (SVGPFDL).

[0078] In still a further exampleaspect, ~~the invention includes~~ CD37-specific SMIP polypeptides with alternative framework regions are described. In one exampleaspect, ~~the invention includes~~ a humanized CD37-specific SMIP polypeptide is described, wherein FR1 of the light chain comprises the amino acid sequence selected from the group consisting of SEQ ID NOS: 170-181. In another exampleaspect, ~~the invention includes~~ a humanized CD37-specific SMIP polypeptide is described, wherein FR1 of the heavy chain comprises the amino acid sequence selected from the group consisting of SEQ ID NOS: 140-146. In a still further exampleaspect, ~~the invention includes~~ a humanized CD37-specific SMIP polypeptide is described, wherein FR2 of the light chain comprises the amino acid sequence selected from the group consisting of SEQ ID NOS: 182-193. In yet another exampleaspect, ~~the invention includes~~ a humanized CD37-specific SMIP polypeptide is described, wherein FR2 of the heavy chain comprises the amino acid sequence selected from the group consisting of SEQ ID NOS: 147-153. In an additional exampleaspect, ~~the invention includes~~ a humanized CD37-specific SMIP polypeptide is described, wherein FR3 of the light chain comprises the amino acid sequence selected from the group consisting of SEQ ID NOS: 194-205. In yet another exampleaspect, ~~the invention includes~~ a humanized CD37-specific SMIP polypeptide is described, wherein FR3 of the

heavy chain comprises the amino acid sequence selected from the group consisting of SEQ ID NOS: 154-160. In a further exampleaspect, the invention includes a humanized CD37-specific SMIP polypeptide is described, wherein FR4 of the light chain comprises the amino acid sequence selected from the group consisting of SEQ ID NOS: 206-210. In yet another exampleaspect, the invention includes a humanized CD37-specific SMIP polypeptide is described, wherein FR4 of the heavy chain comprises the amino acid sequence selected from the group consisting of SEQ ID NOS: 161-169.

[0079] Exemplary CD37-specific SMIPs useful in the invention include, but are not limited to: G28-1 scFv (SSS-S) H WCH2 WCH3, consists of a G28-1 single chain Fv in which all three cysteine residues in the connection or hinge regions are mutated to serine residues, and wild type CH2 and CH3 domains; G28-1 scFv IgAH WCH2 WCH3, comprising an IgA hinge and WT IgG1 domains; G28-1 scFv VHL11S (SSS-S) H WCH2 CH3 in which all three cysteine residues in the connection or hinge regions are mutated to serine residues and the leucine at position 11 of the heavy chain variable region is substituted with a serine; G28-1 scFv VH L11S (CSS-S) H WCH2 CH3, in which cysteine residues were substituted at the second and third positions with serine; G28-1 scFv VHL11S (CSC-S) H WCH2 CH3, in which cysteine residues were substituted at the second position with serine; G28-1 scFv VH11S (SSC-P) H WCH2 WCH3 (referred to as TRU-016 herein), in which the first and second cysteine residues in the connection or hinge regions are mutated to serine residues and the leucine at position 11 of the heavy chain variable region is substituted with a serine; G28-1 scFv VH11S (SCS-S) H WCH2 WCH3, in which the first and third cysteine residues in the hinge regions are mutated to serine residues; G28-1 scFv VHL11S (CCS-P) H WCH2 WCH3, in which the third cysteine residue in the hinge region is substituted with a serine; G28-1scFv VHL11S (SCC-P) H WCH2 WCH3, in which the first cysteine is substituted with a serine; G28-1 scFv VH L11S mIgE CH2 CH3 CH4, comprising mouse IgE CH 2-4 regions in which the leucine at position 11 of the heavy chain variable region is substituted with a serine; G28-1 scFv VH L11S mIgA WIgACH2 T4CH3, comprising a mouse IgA hinge with a wild type IgA CH2 and a truncated IgA CH3 domain lacking

the 4 carboxy amino acids GTCY; G28-1 scFv VHL11S hIgE CH2 CH3 CH4, comprising IgE CH regions in which the leucine at position 11 of the heavy chain variable region is substituted with a serine; and G28-1 scFv VHL11S hIgAH WIgACH2 TCH3, comprising an IgA hinge, a wild type IgA CH2 and a truncated IgA CH2 and a truncated IgA CH3 domain lacking the 4 carboxy amino acids GTCY.

[0080] Exemplary CD20-specific SMIPs ~~useful in the invention~~ include SMIPs derived from the anti-CD20 monoclonal antibody 2H7 described in US Patent Publ. 2003133939. and 20030118592. The SMIPs include 2H7scFv-Ig or a derivative thereof. Derivatives includes CytoxB-MHWTG1C, which has a human IgG1 Fc domain and a mutant IgG1 hinge domain; CytoxB-MHMG1C, which comprises a mutated Fc domain; MG1H/MG1C, which comprises an Fc receptor with a mutated leucine residue 234; CytoxB-IgAHWTHG1C, comprising a portion of the human IgA hinge fused to wild-type human Fc domain; 2H7 scFv-llama IgG1, comprising the llama IgG1 hinge and CH2CH3 regions, 2H7 scFv-llama IgG2, comprising the llama IgG2 hinge and CH2CH3 regions; 2H7 scFv-llama IgG3, comprising the llama IgG3 hinge and CH2CH3 regions.

[0081] 2H7 scFv MTH (SSS) WTCH2CH3, in which all three cysteine residues in the connection or hinge regions are mutated to serine residues, and wild type CH2 and CH3 domains; 2H7 scFv MTH (SSC), in which the first two cysteine residues were substituted with serine residues; 2H7 scFv MTH (SCS), in which the first and third cysteines were substituted with serine residues; 2H7 scFv MTH (CSS) WTCH2CH3, in which cysteine residues were substituted at the second and third positions with serine; 2H7 scFv VH11SER IgG MTH (SSS) WTCH2CH3, in which the leucine at position 11 in the heavy chain variable region is substituted with serine; 2H7 scFv IgA hinge-IgG1 CH2-CH3, comprising an IgA hinge region and WT IgG1 domains; 2H7 scFv IgA hinge-CH2-CH3, comprising IgA hinge, CH2-3 regions; 2H7 IgAWH IgACH2-T4CH3, comprising an IgA hinge, a wild type IgA CH2 and a truncated IgA CH3 domain lacking the 4 carboxy amino acids GTCY.

CH2 WCH3, comprises a mutated hinge region as described above, and a mutated CH2 region in which proline at residue 331 was changed to a serine; 2H7 scFv VH L11S (CSS-S) H P331S CH2 WCH3 comprises a mutated hinge region and a proline to serine mutation at residue 331 in the CH2 region; 2H7 scFv VH L11S (SSS-S) H T256N CH2 WCH3, comprises a mutated hinge region and a threonine to asparagine mutation at residue 256 in the CH2 region; 2H7 scFv VH L11S (SSS-S) H RTPE/QNAK (255-258) CH2 WCH3, comprises a mutated hinge region and a series of mutations in which residues 255-258 have been mutated from arginine, threonine, proline, glutamic acid to glutamine, asparagines, alanine and lysine, respectively; 2H7 scFv VH L11S (SSS-S) H K290Q CH2 WCH3, comprises a mutated hinge regions and a lysine to glutamine change at position 290; 2H7 scFv VH L11S (SSS-S) H A339P CH2 WCH3, comprises a mutated hinge region and an alanine to proline change at position 339; SMIP 2H7 scFv (SSS-S) H P238SCH2 WCH3, comprises a mutated hinge region and an proline to serine change at position 238 in CH2, which is the same as 2H7 scFv IgG MTH (SSS) MTCH2WTCH3. 2H7 scFv IgAH IGAHCH2 T18CH3 comprises a wild type IgA hinge and CH2 region and a CH3 region with an18 amino acid truncation at the carboxy end.

[0085] A binding molecule disclosed hereinof the invention may comprise a native or engineered extracellular domain from another protein which improves the binding molecule activity. In one exampleembodiment, the extracellular domain is selected from the group consisting of CD154 and CTLA4.

[0086] A "synergistic combination" of CD37-specific binding molecules and CD20-specific binding molecules is a combination that has an effect that is greater than the sum of the effects of the binding molecules when administered alone.

[0087] In one exampleaspect of the invention, the binding molecules are administered in one or more pharmaceutical compositions. To administer the binding molecules to human or test animals, it is preferable to formulate the binding molecules in a composition comprising one or more pharmaceutically acceptable carriers. The phrase "pharmaceutically or pharmacologically acceptable" refer to molecular entities and compositions that do not produce

allergic, or other adverse reactions when administered using routes well-known in the art, as described below. "Pharmaceutically acceptable carriers" include any and all clinically useful solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like.

[0088] In addition, compounds may form solvates with water or common organic solvents. Such solvates are contemplated as well.

[0089] The binding molecule compositions may be administered orally, topically, transdermally, parenterally, by inhalation spray, vaginally, rectally, or by intracranial injection. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intracisternal injection, or infusion techniques. Administration by intravenous, intradermal, intramusclar, intramammary, intraperitoneal, intrathecal, retrobulbar, intrapulmonary injection and or surgical implantation at a particular site is contemplated as well. Generally, compositions are essentially free of pyrogens, as well as other impurities that could be harmful to the recipient. Injection, especially intravenous, is preferred.

[0090] Pharmaceutical compositions as described herein~~of the present invention~~ containing binding molecules used in a method disclosed herein~~of the invention~~ may contain pharmaceutically acceptable carriers or additives depending on the route of administration. Examples of such carriers or additives include water, a pharmaceutical acceptable organic solvent, collagen, polyvinyl alcohol, polyvinylpyrrolidone, a carboxyvinyl polymer, carboxymethylcellulose sodium, polyacrylic sodium, sodium alginate, water-soluble dextran, carboxymethyl starch sodium, pectin, methyl cellulose, ethyl cellulose, xanthan gum, gum Arabic, casein, gelatin, agar, diglycerin, glycerin, propylene glycol, polyethylene glycol, Vaseline, paraffin, stearyl alcohol, stearic acid, human serum albumin (HSA), mannitol, sorbitol, lactose, a pharmaceutically acceptable surfactant and the like. Additives used are chosen from, but not limited to, the above or combinations thereof, as appropriate, depending on the dosage form as described herein~~of the present invention~~.

of action. Thus, antibody compositions contemplated are maximally effective when they can be delivered to the site of target antigen activity.

[00100] In one aspect, methods described hereinof the invention include a step of administration of a binding molecule composition.

[00101] Methods described hereinof the invention are performed using any medically-accepted means for introducing a therapeutic directly or indirectly into a mammalian individual, including but not limited to injections, oral ingestion, intranasal, topical, transdermal, parenteral, inhalation spray, vaginal, or rectal administration. The term parenteral as used herein includes subcutaneous, intravenous, intramuscular, and intracisternal injections, as well as catheter or infusion techniques. Administration by, intradermal, intramammary, intraperitoneal, intrathecal, retrobulbar, intrapulmonary injection and or surgical implantation at a particular site is contemplated as well.

[00102] In one exampleembodiment, administration is performed at the site of a cancer or affected tissue needing treatment by direct injection into the site or via a sustained delivery or sustained release mechanism, which can deliver the formulation internally. For example, biodegradable microspheres or capsules or other biodegradable polymer configurations capable of sustained delivery of a composition (*e.g.*, a soluble polypeptide, antibody, or small molecule) can be included in the formulations of the invention implanted near the cancer.

[00103] Therapeutic compositions may also be delivered to the patient at multiple sites. The multiple administrations may be rendered simultaneously or may be administered over a period of time. In certain cases it is beneficial to provide a continuous flow of the therapeutic composition. Additional therapy may be administered on a period basis, for example, hourly, daily, weekly or monthly.

[00104] Binding molecule compositions of the invention may comprise one, or may comprise more than one, binding molecules. Also contemplated by the present disclosureinvention is the administration of binding molecule compositions in

receptors. The above list of construct targets and/or target antigens is exemplary only and is not exhaustive.

[00106] Cytokines and growth factors are second agents contemplated by the invention and include, without limitation, one or more of TNF, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IFN, G-CSF, Meg-CSF, GM-CSF, thrombopoietin, stem cell factor, and erythropoietin. Pharmaceutical compositions described herein~~in accordance with the invention~~ may also include other known angiopoietins, for example Ang-1, Ang-2, Ang-4, Ang-Y, and/or the human angiopoietin-like polypeptide, and/or vascular endothelial growth factor (VEGF). Growth factors for use in pharmaceutical compositions described herein~~of the invention~~ include angiogenin, bone morphogenic protein-1, bone morphogenic protein-2, bone morphogenic protein-3, bone morphogenic protein-4, bone morphogenic protein-5, bone morphogenic protein-6, bone morphogenic protein-7, bone morphogenic protein-8, bone morphogenic protein-9, bone morphogenic protein-10, bone morphogenic protein-11, bone morphogenic protein-12, bone morphogenic protein-13, bone morphogenic protein-14, bone morphogenic protein-15, bone morphogenic protein receptor IA, bone morphogenic protein receptor IB, brain derived neurotrophic factor, ciliary neutrophic factor, ciliary neutrophic factor receptor α, cytokine-induced neutrophil chemotactic factor 1, cytokine-induced neutrophil chemotactic factor 2α, cytokine-induced neutrophil chemotactic factor 2β, β endothelial cell growth factor, endothelin 1, epidermal growth factor, epithelial-derived neutrophil attractant, fibroblast growth factor 4, fibroblast growth factor 5, fibroblast growth factor 6, fibroblast growth factor 7, fibroblast growth factor 8, fibroblast growth factor 8b, fibroblast growth factor 8c, fibroblast growth factor 9, fibroblast growth factor 10, fibroblast growth factor acidic, fibroblast growth factor basic, glial cell line-derived neutrophic factor receptor α1, glial cell line-derived neutrophic factor receptor α2, growth related protein, growth related protein α, growth related protein β, growth related protein γ, heparin binding epidermal growth factor, hepatocyte growth factor, hepatocyte growth factor receptor, insulin-like growth factor I, insulin-like growth factor receptor, insulin-like growth factor II, insulin-like growth factor binding protein, keratinocyte growth factor, leukemia inhibitory factor,

zinc phthalocyanines

Androgens
testosterone propionate
fluoxymesterone/equivalents

Antiandrogens
flutamide
gonadotropin-releasing
hormone analogs
leuprolide

Nonsteroidal antiandrogens
flutamide

Radiation
X-ray
ultraviolet light
gamma radiation
visible light
infrared radiation
microwave radiation

[00109] Second agents contemplated by the disclosure~~invention~~ for treatment of autoimmune diseases are referred to as immunosuppressive agents, which act to suppress or mask the immune system of the individual being treated. Immunosuppressive agents include, for example, non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, glucocorticoids, disease-modifying antirheumatic drugs (DMARDs) for the treatment of arthritis, or biologic response modifiers. Compositions in the DMARD description are also useful in the treatment of many other autoimmune diseases aside from RA.

[00110] Exemplary NSAIDs are chosen from the group consisting of ibuprofen, naproxen, naproxen sodium, Cox-2 inhibitors such as Vioxx and Celebrex, and sialylates. Exemplary analgesics are chosen from the group consisting of acetaminophen, oxycodone, tramadol of proporxyphene hydrochloride. Exemplary glucocorticoids are chosen from the group consisting of cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, or prednisone. Exemplary biological response modifiers include, but are not limited to, molecules directed against cell surface markers (e.g., CD4, CD5, etc.), cytokine inhibitors, such as the TNF antagonists (e.g. etanercept (Enbrel), adalimumab (Humira) and infliximab (Remicade)), chemokine inhibitors and adhesion molecule inhibitors. The biological response modifiers include monoclonal antibodies as well as recombinant forms of molecules. Exemplary DMARDs include, but are not limited to, azathioprine, cyclophosphamide, cyclosporine, methotrexate, penicillamine,

leflunomide, sulfasalazine, hydroxychloroquine, Gold [oral (auranofin) and intramuscular] and minocycline.

[00111] It is contemplated the binding molecule composition and the second agent may be given simultaneously in the same formulation. Alternatively, the agents are administered in a separate formulation but concurrently, with concurrently referring to agents given within 30 minutes of each other.

[00112] In another example~~aspect~~, the second agent is administered prior to administration of the binding molecule composition. Prior administration refers to administration of the second agent within the range of one week prior to treatment with the antibody, up to 30 minutes before administration of the antibody. It is further contemplated that the second agent is administered subsequent to administration of the binding molecule composition. Subsequent administration is meant to describe administration from 30 minutes after antibody treatment up to one week after antibody administration.

[00113] It is further contemplated that when the binding molecule is administered in combination with a second agent, wherein the second agent is a cytokine or growth factor, or a chemotherapeutic agent, the administration may also include use of a radiotherapeutic agent or radiation therapy. The radiation therapy administered in combination with an antibody composition is administered as determined by the treating physician, and at doses typically given to patients being treated for cancer.

[00114] The amounts of binding molecule in a given dose will vary according to the size of the individual to whom the therapy is being administered as well as the characteristics of the disorder being treated. In exemplary treatments, it may be necessary to administer about 1 mg/day, about 5 mg/day, about 10 mg/day, about 20 mg/day, about 50 mg/day, about 75 mg/day, about 100 mg/day, about 150 mg/day, about 200 mg/day, about 250 mg/day, about 500 mg/day or about 1000 mg/day. The doses may also be administered based on weight of the patient, at a dose of about 0.01 to about 50 mg/kg. In a related example~~embodiment~~, the binding molecule may be administered in a dose range of about 0.015 to about 30 mg/kg. In an

additional embodiment, the binding molecule is administered in a dose of about 0.015, about 0.05, about 0.15, about 0.5, about 1.5, about 5, about 15 or about 30 mg/kg.

[00115] These compositions may be administered in a single dose or in multiple doses. Standard dose-response studies, first in animal models and then in clinical testing, reveal optimal dosages for particular disease states and patient populations.

[00116] The administration of the binding molecule composition decreases the B-cell population by at least 20% after a single dose of treatment. In one embodiment, the B-cell population is decreased by at least about 20, about 30, about 40, about 50, about 60, about 70, about 80, about 90 or about 100%. B-cell reduction is defined as a decrease in absolute B-cell count below the lower limit of the normal range. B-cell recovery is defined as a return of absolute B-cell count to either of the following: 70% of subject's baseline value or normal range.

[00117] The administration of CD20-specific binding molecules also results in enhanced apoptosis in particular B-cell subsets. Apoptosis refers to the induction of programmed cell death of a cell, manifested and assessed by DNA fragmentation, cell shrinkage, cell fragmentation, formation of membrane vesicles, or alteration of membrane lipid composition as assessed by annexin V staining.

[00118] Further, the administration of binding molecule compositions described hereinof the invention results in desired clinical effects in the disease or disorder being treated. For example, in patients affected by rheumatoid arthritis, in one exampleaspect the administration improves the patient's condition by a clinically significant amount [e.g., achieves the American College of Rheumatology Preliminary Detection of Improvement (ACR20)], and/or an improvement of 20% in tender and swollen joint and 20% improvement in 3/5 remaining ACR measures (Felson et al., *Arthritis Rheum.* 1995, 38:727-35). Biological measures for improvement in an RA patient after administration of CD37-specific and CD20-specific binding molecules include measurement of changes in cytokine levels, measured via protein or RNA levels. Cytokines of

interest include, but are not limited to, TNF-α, IL-1, interferons, Blys, and APRIL. Cytokine changes may be due to reduced B cell numbers or decreased activated T cells. In RA patients, markers relevant to bone turnover (bone resorption or erosion) are measured before and after administration of CD20-specific binding molecules. Relevant markers include, but are not limited to, alkaline phosphatase, osteocalcin, collagen breakdown fragments, hydroxyproline, tartrate-resistant acid phosphatase, and RANK ligand (RANKL). Other readouts relevant to the improvement of RA include measurement of C reactive protein (CRP) levels, erythrocyte sedimentation rate (ESR), rheumatoid factor, CCP (cyclic citrullinated peptide) antibodies and assessment of systemic B cell levels and lymphocyte count via flow cytometry. Specific factors can also be measured from the synovium of RA patients, including assessment of B cell levels in synovium from synovium biopsy, levels of RANKL and other bone factors and cytokines set out above.

[00119] In a related exampleaspect, the effects of combination administration on other diseases is measured according to standards known in the art. For example, it is contemplated that Crohn's disease patients treated according to the invention achieve an improvement in Crohn's Disease Activity Index (CDAI) in the range of about 50 to about 70 units, wherein remission is at 150 units (Simonis et al, *Scand. J Gastroent.* 1998, 33:283-8). A score of 150 or 200 is considered normal, while a score of 450 is considered a severe disease score. It is further desired that administration of the CD37-specific and CD20-specific binding molecules results in a reduction in perinuclear anti-neutrophil antibody (pANCA) and anti-Saccharomyces cervisiae antibody (ASCA) in individuals affected by inflammatory bowel disease.

[00120] It is further contemplated that adult and juvenile myositis patients treated as described hereinaccording to the invention achieve an improvement in core set of evaluations, such as 3 out of 6 of the core set measured improved by approximately 20%, with not more than 2 of the core measurements worse by approximately 25% (see Rider et al., *Arthritis Rheum.* 2004, 50:2281-90).

[00121] It is further contemplated that SLE patients treated as described hereinaccording to the invention achieve an improvement in Systemic Lupus Activity Measure

(SLAM) or SLE Disease Activity Index (SLEDAI) score of at least 1 point (Gladman et al, *J Rheumatol* 1994, 21:1468-71) (Tan et al., Arthritis Rheum. 1982, 25:1271-7). A SLAM score of >5, or SLEDAI score >2, is considered clinically active disease. A response to treatment may be defined as improvement or stabilization over the in 2 disease activity measures (the SLE Disease Activity Index [SLEDAI] and the Systemic Lupus Activity Measure) and 2 quality of life measures (patient's global assessment and the Krupp Fatigue Severity Scale) (Petri et al., *Arthritis Rheum.* 2004, 50:2858-68.) It is further contemplated that administration of the binding molecule to SLE patients results in a reduction in anti-double-stranded DNA antibodies. Alternatively, improvement may be gauged using the British Isles Lupus Assessment Group Criteria (BILAG).

[00122] It is further contemplated that multiple sclerosis patients treated as described hereinaccording to the invention achieve an improvement in clinical score on the Kurtzke Expanded Disability status scale (EDSS) (Kurtzke, F., *Neurology* 1983, 33:1444-52) of at least 0.5, or a delay in worsening of clinical disease of at least 1.0 on the Kurtzke scale (Rudick et al., *Neurology* 1997, 49:358-63).

[00123] It is further contemplated that patients suffering from IIM receiving CD37-specific and CD20-specific binding molecules achieve a reduction in at least one of five criteria set out in the Idiopathic Inflammatory Myopathy Criteria (IIMC) assessment (Miller, F., *supra*). It is further contemplated that administration to IIM patients results in a reduction in IIM associated factors selected from the group consisting of creatine kinase (CK), lactate dehydrogenase, aldolase, C-reactive protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and antinuclear autoantibody (ANA), myositis-specific antibodies (MSA), and antibody to extractable nuclear antigens. Alternatively, patients meet 3 out of 6 of the criteria set out in Rider et al., Arthritis Rheum., 50(7):2281-2290 (2004), with worsening in no more than 2 criteria.

[00124] In some examplesembodiments, patients suffering from a B cell cancer receive treatment as described hereinaccording to the invention and demonstrate an overall beneficial response to the treatment, based on clinical criteria well-known and

[00127] Typically, the grade of lymphoma is clinically assessed using the criterion that low-grade lymphoma usually presents as a nodal disease and is often indolent or slow-growing. Intermediate- and high-grade disease usually presents as a much more aggressive disease with large extranodal bulky tumors.

[00128] The Ann Arbor classification system is also used to measure progression of tumors, especially non-Hodgkins lymphomas. In this system, stages I, II, III, and IV of adult NHL can be classified into A and B categories depending on whether the patient has well-defined generalized symptoms (B) or not (A). The B designation is given to patients with the following symptoms: unexplained loss of more than 10% body weight in the 6 months prior to diagnosis, unexplained fever with temperatures above 38° C. and drenching night sweats. Definitions of the stages are as follows: Stage I-involvement of a single lymph node region or localized involvement of a single extralymphatic organ or site. Stage II-involvement of two or more lymph node regions on the same side of the diaphragm or localized involvement of a single associated extralymphatic organ or site and its regional lymph nodes with or without other lymph node regions on the same side of the diaphragm. Stage III-involvement of lymph node regions on both sides of the diaphragm, possibly accompanying localized involvement of an extralymphatic organ or site, involvement of the spleen, or both. Stage IV-disseminated (multifocal) involvement of one or more extralymphatic sites with or without associated lymph node involvement or isolated extralymphatic organ involvement with distant (non-regional) nodal involvement. For further details, see The International Non-Hodgkin's Lymphoma Prognostic Factors Project: A predictive model for aggressive non-Hodgkin's lymphoma, New England J. Med. (1993) 329:987-994.

[00129] In one example~~aspect~~, a therapeutic effect of the methods as described herein~~according to the invention~~ is determined by the level of response, for example a partial response is defined as tumor reduction to less than one-half of its original size. A complete response is defined as total elimination of disease confirmed by clinical or radiological evaluation. In one example~~embodiment~~, the

individual receiving treatment as described herein~~according to the invention~~ demonstrates at least a partial response to treatment.

[00130] According to the Cheson criteria for assessing NHL developed in collaboration with the National Cancer Institute (Cheson et al., *J Clin Oncol.* 1999, 17:1244; Grillo-Lopez et al., *Ann Oncol.* 2000, 11:399-408), a complete response is obtained when there is a complete disappearance of all detectable clinical and radiographic evidence of disease and disease-related symptoms, all lymph nodes have returned to normal size, the spleen has regressed in size, and the bone marrow is cleared of lymphoma.

[00131] An unconfirmed complete response is obtained when a patient shows complete disappearance of the disease and the spleen regresses in size, but lymph nodes have regressed by more than 75% and the bone marrow is indeterminate. An unconfirmed complete response meets and exceeds the criteria for partial response. An overall response is defined as a reduction of at least 50 percent in overall tumor burden.

[00132] Similar criteria have been developed for various other forms of cancers or hyperproliferative diseases and are readily available to a person of skill in the art. See, e.g., Cheson et al., *Clin Adv Hematol Oncol.* 2006, 4:4-5, which describes criteria for assessing CLL; Cheson et al., *J Clin Oncol.* 2003, 21:4642-9, which describes criteria for AML; Cheson et al., *Blood* 2000, 96:3671-4, which describes criteria for myelodysplastic syndromes.

[00133] In another example~~aspect~~, a therapeutic response in patients having a B cell cancer is manifest as a slowing of disease progression compared to patients not receiving therapy. Measurement of slowed disease progression or any of the above factors may be carried out using techniques well-known in the art, including bone scan, CT scan, gallium scan, lymphangiogram, MRI, PET scans, ultrasound, and the like.

[00134] It will also be apparent that dosing may be modified if traditional therapeutics are administered in combination with therapeutics disclosed herein~~of the invention~~.

[00135] As an additional exampleaspect, the invention includes kits are described which comprise one or more compounds or compositions useful in the methods described hereinof the invention packaged in a manner which facilitates their use to practice methods disclosed hereinof the invention. In a simplest exampleembodiment, such a kit includes a compound or composition described herein as useful for practice of a method disclosed hereinof the invention packaged in a container such as a sealed bottle or vessel, with a label affixed to the container or included in the package that describes use of the compound or composition to practice the method described hereinof the invention. Preferably, the compound or composition is packaged in a unit dosage form. The kit may further include a device suitable for administering the composition according to a preferred route of administration or for practicing a screening assay. The kit may include a label that describes use of the binding molecule composition(s) in a method disclosed hereinof the invention.

[00136] The disclosurepresent invention also comprises articles of manufacture. Such articles comprise CD37-specific binding molecules or CD37-specific and CD20-specific binding molecules, optionally together with a pharmaceutical carrier or diluent, and at least one label describing a method of use of the binding molecules described hereinaccording to the invention. Such articles of manufacture may also optionally comprise at least one second agent for administration in connection with the binding molecules.

[00137] The present disclosureinvention also calls for use of a composition comprising a CD37-specific binding molecule or CD37-specific and CD20-specific binding molecules in the manufacture of a medicament for the treatment or prophylaxis of a disease involving aberrant B-cell activity.

BRIEF DESCRIPTION OF THE DRAWING

[00138] Figure 1A diagrams the structure of the TRU-016 molecule; Figure 1B shows the results of SDS-PAGE analysis, demonstrating that the expressed protein migrates at a Mr of approximately 110 kDa under nonreducing conditions, and approximately 52 kDa when subjected to reducing conditions; and Figure 1C shows that the TRU-016 molecule