Office de la Propriété Intellectuelle du Canada
Un organisme d'Industrie Canada

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2719924 C 2017/10/03

(11)(21) 2 719 924

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 2009/04/11
(87) Date publication PCT/PCT Publication Date: 2009/10/15
(45) Date de délivrance/Issue Date: 2017/10/03
(85) Entrée phase nationale/National Entry: 2010/09/28
(86) N° demande PCT/PCT Application No.: US 2009/040288
(87) N° publication PCT/PCT Publication No.: 2009/126944
(30) Priorité/Priority: 2008/04/11 (US61/190,067)

(51) Cl.Int./Int.Cl. *C07K 16/28* (2006.01), *A61K 31/4184* (2006.01), *A61K 39/395* (2006.01), *A61P 35/02* (2006.01), *C12N 15/02* (2006.01)

(72) Inventeurs/Inventors:
TAN, PHILIP, US;
SIMON, SANDY ALEXANDER, US;
CERVENY, CHARLES G., US;
NILSSON, CHRISTY ANNE, US;
BRADY, WILLIAM, US;
LEDBETTER, JEFFREY A., US;
...

(73) Propriétaire/Owner:

(54) Titre : PRODUITS D'IMMUNOTHERAPIE DE CD37 ET COMBINAISON AVEC UN PRODUIT CHIMIOTHERAPIQUE BIFONCTIONNEL DE CELUI-CI

(54) Title: CD37 IMMUNOTHERAPEUTIC AND COMBINATION WITH BIFUNCTIONAL CHEMOTHERAPEUTIC THEREOF

HEAVY CHAIN

	FR1	CDR1	FR2	CDR2
G28-1	AVQLQQSGPESEKPGASVKISCKASGYSFT	GYNMN	WVKQNNGKSLEWIG	NIDPYYGGTTYNRKFKG
CAS-024	EVQLVQSGAEVKKPGESLKISCKGSGYSFT	GYNMN	WVRQMPGKGLEWMG	NIDPYYGGTTYNRKFKG
Consensus	-VQL-QSG-E--KPG-S-KISCK-SGYSFT	GYNMN	WV-Q--GK-LEW-G	NIDPYYGGTTYNRKFKG

	FR3	CDR3	FR4
G28-1	KATLTVDKSSSTAYMQLKSLTSEDSAVYYCAR	SVGPMDY	WGQGTSVTVSS
CAS-024	QVTISADKSISTAYLQWSSLKASDTAMYYCAR	SVGPFDS	WGQGTLVTVSS
Consensus	--T---DKS-STAY-Q--SL---D-A-YYCAR	SVGP-D-	WGQGT-VTVSS

LIGHT CHAIN

	FR1	CDR1	FR2	CDR2
G28-1	DIQMTQSPASLSASVGETVTITC	RTSENVYSYLA	WYQQKQGKSPQLLVS	FAKTLAE
CAS-024	EIVLTQSPATLSLSPGERATLSC	RASENVYSYLA	WYQQKPGQAPRLLIY	FAKTLAE
Consensus	-I--TQSPATLS-S-GE--T--C	R-SENVYSYLA	WYQQK-G--P-LL--	FAKTLAE

	FR3	CDR3	FR4
G28-1	GVPSRFSGSGSGTQFSLKISSLQPEDSGSYFC	QHHSDNPWT	FGGGTELEIK
CAS-024	GIPARFSGSGSGTDFTLTISSLEPEDFAVYYC	QHHSDNPWT	FGQGTKVEIK
Consensus	G-P-RFSGSGSGT-F-L-ISSL-PED---Y-C	QHHSDNPWT	FG-GT--EIK

(57) Abrégé/Abstract:
The present disclosure provides a humanized anti-CD37 small modular immunopharmaceutical (SMIP) molecule, as well as synergistic combination therapies of CD37-specific binding molecules (such as anti-CD37 SMIP proteins or antibodies) with

CA 2719924 C 2017/10/03

(11)(21) 2 719 924

(13) C

(72) Inventeurs(suite)/Inventors(continued): HAYDEN-LEDBETTER, MARTHA SUSAN, US;
THOMPSON, PETER ARMSTRONG, US; MORALES, CECILE, US

(73) Propriétaires(suite)/Owners(continued):APTEVO RESEARCH AND DEVELOPMENT LLC, US

(74) Agent: SMART & BIGGAR

(57) Abrégé(suite)/Abstract(continued):
bifunctional chemotherapeutics (such as bendamustine) that can be administered concurrently or sequentially, for use in treating or preventing B cell related autoimmune, inflammatory, or hyperproliferative diseases.

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 October 2009 (15.10.2009)

PCT

(10) International Publication Number
WO 2009/126944 A1

(51) International Patent Classification:
C07K 16/28 (2006.01) *A61K 31/4184* (2006.01)
A61K 39/395 (2006.01) *A61P 35/02* (2006.01)
C12N 15/02 (2006.01)

(21) International Application Number:
PCT/US2009/040288

(22) International Filing Date:
11 April 2009 (11.04.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/190,067 11 April 2008 (11.04.2008) US

(71) Applicant *(for all designated States except US)*: **TRUBION PHARMACEUTICALS, INC.** [US/US]; 2401 Fourth Avenue, Suite 1050, Seattle, WA 98121 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **TAN, Phillip** [US/US]; 17409 53rd Place West, Lynnwood, WA 98037 (US). **SIMON, Sandy, Alexander** [US/US]; 1904 Northeast 68th Street, Seattle, WA 98115 (US). **CERVENY, Charles, G.** [US/US]; 339 Northeast 91st Street, Seattle, WA 98115 (US). **NILSSON, Christy, Anne** [US/US]; 1105 235th Place Northeast, Sammamish, WA 98074 (US). **BRADY, William** [US/US]; 618 219th Place Southwest, Bothell, WA 98021 (US). **LEDBETTER, Jeffrey, A.** [US/US]; 18798 Ridgefield Road Northwest, Shoreline, WA 98177 (US). **HAYDEN-LEDBETTER, Martha, Susan** [US/US]; 18798 Ridgefield Road Northwest, Shoreline, WA 98177 (US). **THOMPSON, Peter, Armstrong** [US/US]; 14075 Northeast 30th Place, Bellevue, WA 98007 (US). **MORALES, Cecile** [US/US]; 1920 Nob Hill Avenue North, Seattle, WA 98109 (US).

(74) Agents: **LIN, Qing** et al.; Seed Intellectual Property Law Group PLLC, Suite 5400, 701 Fifth Avenue, Seattle, WA 98104-7064 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: CD37 IMMUNOTHERAPEUTIC AND COMBINATION WITH BIFUNCTIONAL CHEMOTHERAPEUTIC THEREOF

HEAVY CHAIN

	FR1	CDR1	FR2	CDR2
G28-1	AVQLQQSGPESEKPGASVKISCKASGYSFT	GYNMN	WVKQNNGKSLEWIG	NIDPYYGGTTYNRKFKG
CAS-024	EVQLVQSGAEVKKPGESLKISCKGSGYSFT	GYNMN	WVRQMPGKGLEWMG	NIDPYYGGTTYNRKFKG
Consensus	-VQL-QSG-E--KPG-S-KISCK-SGYSFT	GYNMN	WV-Q--GK-LEW-G	NIDPYYGGTTYNRKFKG

	FR3	CDR3	FR4
G28-1	KATLTVDKSSSTAYMQLKSLTSEDSAVYYCAR	SVGPMDY	WGQGTSVTVSS
CAS-024	QVTISADKSISTAYLQWSSLKASDTAMYYCAR	SVGPFDS	WGQGTLVTVSS
Consensus	--T---DKS-STAY-Q--SL---D-A-YYCAR	SVGP-D-	WGQGT-VTVSS

LIGHT CHAIN

	FR1	CDR1	FR2	CDR2
G28-1	DIQMTQSPASLSASVGETVTITC	RTSENVYSYLA	WYQQKQGKSPQLLVS	FAKTLAE
CAS-024	EIVLTQSPATLSLSPGERATLSC	RASENVYSYLA	WYQQKPGQAPRLLIY	FAKTLAE
Consensus	-I--TQSPATLS-S-GE--T--C	R-SENVYSYLA	WYQQK-G--P-LL--	FAKTLAE

	FR3	CDR3	FR4
G28-1	GVPSRFSGSGSGTQFSLKISSLQPEDSGSYFC	QHHSDNPWT	FGQGTKVEIK
CAS-024	GIPARFSGSGSGTDFTLTISSLEPEDFAVYYC	QHHSDNPWT	FGQGTKVEIK
Consensus	G-P-RFSGSGSGT-F-L-ISSL-PED---Y-C	QHHSDNPWT	FGQGTKVEIK

Fig. 1

(57) Abstract: The present disclosure provides a humanized anti-CD37 small modular immunopharmaceutical (SMIP) molecule, as well as synergistic combination therapies of CD37-specific binding molecules (such as anti-CD37 SMIP proteins or antibodies) with bifunctional chemotherapeutics (such as bendamustine) that can be administered concurrently or sequentially, for use in treating or preventing B cell related autoimmune, inflammatory, or hyperproliferative diseases.

WO 2009/126944 A1

WO 2009/126944 A1

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

— *with sequence listing part of description (Rule 5.2(a))*

CD37 IMMUNOTHERAPEUTIC AND COMBINATION WITH BIFUNCTIONAL CHEMOTHERAPEUTIC THEREOF

BACKGROUND

Technical Field

The present disclosure generally provides compositions and methods for treating B-cell disorders and, more specifically, a humanized anti-CD37 small modular immunopharmaceutical (SMIP) molecule, as well as synergistic combination therapies of CD37-specific binding molecules with bifunctional chemotherapeutics for use in treating or preventing B-cell related autoimmune, inflammatory, or hyperproliferative diseases.

Description of the Related Art

The human immune system generally protects the body from invading foreign substances and pathogens. One component of the immune system is B lymphocytes, also referred to as B-cells, which produce antibodies that protect the body by binding to, and in some cases mediating destruction of, a foreign substance or pathogen. In some instances, however, the immune system

functions can go awry and disease results. For example, there are numerous cancers, autoimmune diseases, and inflammatory diseases that involve uncontrolled proliferation of B-cells.

B-cells can be identified by molecules on their cell surface, such as CD37. CD37 is a heavily glycosylated 40-52 kDa protein that belongs to the tetraspanin transmembrane family of cell surface antigens, which is highly expressed on normal antibody-producing B-cells but not on pre-B-cells or plasma cells. In addition to normal B-cells, almost all malignancies of B-cell origin are positive for CD37 expression, including chronic lymphocytic leukemia (CLL), non-Hodgkins lymphoma (NHL), and hairy cell leukemia (Moore *et al.*, J. Pathol. 152:13 (1987); Merson and Brochier, Immunol. Lett. 19:269 (1988); and Faure *et al.*, Am. J. Dermatopathol. 12:122 (1990)).

A few CD37 specific immunotherapies have been developed. An IgG1 murine monoclonal antibody specific for CD37, MB-1, was labeled with ^{131}I and tested in a clinical trial in the treatment of NHL (*see* Press *et al.*, J. Clin. Oncol. 7:1027 (1989); Bernstein *et al.*, Cancer Res. (Suppl.) 50:1017 (1990); Press *et al.*, Front. Radiat. Ther. Oncol. 24:204 (1990); Press *et al.*, Adv. Exp. Med. Biol. 303:91 (1991) and Brown *et al.*, Nucl. Med. Biol. 24:657 (1997)). The MB-1 antibody lacks Fc effector functions, such as antibody-dependent cellular cytotoxicity (ADCC), and the naked MB-1 antibody did not inhibit tumor growth in an *in vivo* xenograft model (Buchsbaum *et al.*, Cancer Res. 52:6476 (1992)). In addition, an immunoconjugate having adriamycin linked to G28-1, another murine monoclonal anti-CD37, was administered to mice and shown to be internalized with adriamycin being released intracellularly (*see*, Braslawsky *et al.*, Cancer Immunol. Immunother. 33:367 (1991)). An engineered fusion protein, termed a small modular immunopharmaceutical (SMIP™) product, directed to CD37 is currently being tested in humans (*see*, *e.g.*, US Patent Application Publications 2003/0133939 and 2007/0059306).

Although there has been extensive research carried out on antibody-based therapies, there remains a need in the art for alternative or improved compositions and methods for treating B-cell associated disorders or diseases.

BRIEF SUMMARY

In one aspect, the present disclosure provides humanized CD37-specific binding molecules and a method for reducing B-cells or treating a disease associated with aberrant B-cell activity comprising administering to a subject in need thereof an effective amount of a humanized CD37-specific binding molecule provided herein.

In certain embodiments, the present disclosure provides a humanized CD37-specific binding molecule, comprising from amino terminus to carboxyl terminus: (i) a humanized heavy chain variable region, (ii) a linker as set forth in SEQ ID NO:229, (iii) a humanized light chain variable region, (iv) an IgG1 hinge, (v) human IgG1 CH2 region, and (vi) human IgG1 CH3 region, wherein (a) the humanized heavy chain variable region comprises from amino terminus to carboxyl terminus: a humanized heavy chain FR1, a heavy chain CDR1 as set forth in SEQ ID NO:63, a humanized heavy chain FR2, a heavy chain CDR2 as set forth in SEQ ID NO:65, a humanized heavy chain FR3, a heavy chain CDR3 as set forth in SEQ ID NO:67, 68 or 69, and a humanized heavy chain FR4, and (b) the humanized light chain variable region comprises from amino terminus to carboxyl terminus: a humanized light chain FR1, a light chain CDR1 as set forth in SEQ ID NO:61 or 62, a humanized light chain FR2, a light chain CDR2 as set forth in SEQ ID NO:64, a humanized light chain FR3, and a light chain CDR3 as set forth in SEQ ID NO:66, and a humanized light chain FR4.

In certain embodiments of the above humanized CD37-sepcific binding molecules, the humanized heavy chain FR1 comprises SEQ ID NO:144, the humanized heavy chain FR2 comprises SEQ ID NO:151, the heavy chain FR3 comprises SEQ ID NO:158, and the heavy chain FR4 comprises SEQ ID NO:161 or 162.

In certain embodiments of any one of the above humanized CD37-specific binding molecules, the humanized light chain FR1 comprises SEQ ID NO:171, the light chain FR2 comprises SEQ ID NO:182, the light chain FR3 comprises SEQ ID NO:195, and the light chain FR4 comprises SEQ ID NO:206.

In a related aspect, the present disclosure provides a CD37-specific binding molecule that comprises the amino acid sequence as set forth in SEQ ID NO:253.

In certain embodiments, the CD37-specific binding molecule consists essentially of the amino acid sequence as set forth in SEQ ID NO:253.

In certain embodiments, the CD37-specific binding molecule consists of the amino acid sequence as set forth in SEQ ID NO:253.

In a related aspect, the present disclosure also provides an isolated nucleic acid molecule that comprises a nucleotide sequence encoding a humanized CD37-sepcific binding molecule provided herein.

In another related aspect, the present disclosure provides a vector that comprises an isolated nucleic acid molecule that encodes a humanized CD37-sepcific binding molecule provided herein.

In another related aspect, the present disclosure provides a host cell that comprises the above-described vector.

The present disclosure also provides a composition that comprises a humanized CD37-specific binding molecule provided herein and a pharmaceutically acceptable carrier.

In another aspect, the present disclosure provides a method for reducing B-cells or treating a disease associated with aberrant B-cell activity, comprising administering to a subject in need thereof an effective amount of a humanized CD37-specific binding molecule provided herein.

In certain embodiments, the disease associated with aberrant B-cell activity is a B-cell lymphoma, a B-cell leukemia, a B-cell myeloma, a disease characterized by autoantibody production, or a disease characterized by inappropriate T-cell stimulation associated with a B-cell pathway.

In certain embodiments, the disease characterized by autoantibody production is idiopathic inflammatory myopathy, rheumatoid arthritis, myasthenia gravis, Grave's disease, type I diabetes mellitus, multiple sclerosis, an autoimmune disease, dermatomyositis, polymyositis, or Waldenstrom's macroglobinemia.

In certain embodiments, the disease associated with aberrant B-cell activity is chronic lymphocytic leukemia (CLL).

In another aspect, the present disclosure provides compositions and methods for the combined use of CD37-specific binding molecules and bifunctional chemotherapeutics to reduce B-cells or treat a disease associated with aberrant B-cell activity. A surprising result of this combination is that these compounds act synergistically, which results in an increased B-cell reduction.

For example, the present disclosure provides a composition that comprises a CD37-specific binding molecule and bendamustine.

In certain embodiments, the CD37-specific binding molecule is a CD37-specific antibody or SMIP, such as a humanized antibody or humanized SMIP.

In certain embodiments, the CD37-specific binding molecule competes with G28-1 mAb in CD37-specific binding.

In certain embodiments, the CD37-specific binding molecule is a humanized CD37-specific binding molecule provided herein, such as a humanized CD37-specific binding molecule that comprises, consists essentially of, or consists of, the amino acid sequence as set forth in SEQ ID NO:253.

In a related aspect, the present disclosure provides a method for reducing B-cells or treating a disease associated with aberrant B-cell activity, comprising administering to a subject in need thereof an effective amount of a CD37-specific binding molecule and bendamustine.

In certain embodiments, the disease associated with aberrant B-cell activity is a B-cell lymphoma, a B-cell leukemia, a B-cell myeloma, a disease characterized by autoantibody production, or a disease characterized by inappropriate T-cell stimulation associated with a B-cell pathway.

In certain further embodiments, the disease characterized by autoantibody production is idiopathic inflammatory myopathy, rheumatoid arthritis, myasthenia gravis, Grave's disease, type I diabetes mellitus, multiple sclerosis, an autoimmune disease, dermatomyositis, polymyositis, or Waldenstrom's macroglobinemia.

In certain other embodiments, the disease associated with aberrant B-cell activity is chronic lymphocytic leukemia (CLL).

In certain embodiments, the CD37-specific binding molecule and bendamustine are administered concurrently.

In certain other embodiments, the CD37-specific binding molecule and bendamustine are administered sequentially.

In certain embodiments, the CD37-sepcific binding molecule and bendamustine are formulated together.

In certain embodiments, the CD37-specific binding molecule is a CD37-specific antibody or SMIP, such as a humanized antibody or a humanized SMIP.

In certain embodiments, the CD37-specific binding molecule competes with G28-1 mAb in CD37-specific binding.

In certain embodiments, the CD37-specific binding molecule is a humanized CD37-specific binding molecule provided herein, such as a humanized CD37-specific binding molecule that comprises, consists essentially of, or consists of, the amino acid sequence as set forth in SEQ ID NO:253.

The claimed invention relates to a humanized CD37-specific binding molecule, comprising from amino terminus to carboxyl terminus: (i) a humanized heavy chain variable region, (ii) a linker as set forth in SEQ ID NO:229, (iii) a humanized light chain variable region, (iv) an IgG1 hinge, (iv) human IgG1 CH2 region, and (vi) human IgG1 CH3 region, wherein (a) the humanized heavy chain variable region comprises from amino terminus to carboxyl terminus: a human heavy chain FR1, a heavy chain CDR1 as set forth in SEQ ID NO:63, a human heavy chain FR2, a heavy chain CDR2 as set forth in SEQ ID NO:65, a human heavy chain FR3, a heavy chain CDR3 as set forth in SEQ ID NO:67, 68 or 69, and a human heavy chain FR4, and (b) the humanized light chain variable region comprises from amino terminus to carboxyl terminus: a human light chain FR1, a light chain CDR1 as set forth in SEQ ID NO:61 or 62, a human light chain FR2, a light chain CDR2 as set forth in SEQ ID NO:64, a human light chain FR3, and a light chain CDR3 as set forth in SEQ ID NO:66, and a human light chain FR4. Also claimed is an isolated nucleic acid molecule comprising a nucleotide sequence encoding such a binding molecule, vectors comprising such a nucleic acid molecule and host cells

comprising such a vector. Also claimed is a composition comprising such a binding molecule and a pharmaceutically acceptable carrier. Such a binding molecule or composition can be used for reducing B-cells and such a binding molecule or composition may be for use in treating a disease associated with aberrant B-cell activity or in preparation of a medicament for such treating, as described herein.

The claimed invention also relates to a composition comprising a CD37-specific binding molecule as claimed herein and bendamustine. Such a composition may be for use in reducing B-cells. Also claimed is use of such a binding molecule and bendamustine for reducing B-cells or in preparation of a medicament or a combination of medicaments for reducing B-cells. Such a composition or medicament may be for use in treating a disease associated with aberrant B-cell activity, as described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows heavy and light chain variable region amino acid sequence alignments of mouse G28.1 and CAS-024 sequences, along with a consensus identity sequence.

Figures 2A-2D show the size exclusion chromatography (SEC) chromatograms of CAS-001, CAS-002, CAS-003, and CAS-024. The peaks of interest (POI) have 98-99% of the SMIP molecules being purified. CAS-024 has a very sharp and symmetrical peak (indicating homogeneity), whereas CAS-001, CAS-002, and CAS-003 peaks have a slight shoulder (where upon integration, the shoulder accouts for about 35% of the POI), which indicates a heterogenous population of molecules.
Figure 3 is graph showing how various anti-CD37 specific SMIP proteins compete with the parent CAS-006 molecule (chimeric anti-CD37 SMIP protein, mVLmVH) for binding to CD37 on Ramos cells, which provides an

indication on the affinity of binding as compared to the parent molecule. CAS-024 (hVHhVL) has substantially the same affinity for CD37 as does CAS-006, whereas the other molecules (CAS-001, CAS-002, and CAS-003, all hVLhVH) have a 2- to 4-fold decrease in affinity.

Figures 4A and 4B are graphs of additional binding competition assays against CAS-006 (labeled as SMIP-016 in these graphs). Here, mouse-human hybrid SMIP molecules (CAS-014 mVHhVL and CAS-017 hVLmVH) have an affinity that is higher than CAS-006, whereas CAS-024 shows the same binding affinity as CAS-006 and CAS-003 (hVLhVH) has a lower binding affinity.

Figures 5A-5E show competitive binding between various different anti-CD37 antibodies and CAS-006 (a chimeric anti-CD37 SMIP molecule).

Figures 6A and 6B show that CAS-024 was statistically superior to Rituxan® in the *in vivo* treatment of an animal model of follicular lymphoma as shown by (A) survival rate and (B) tumor-free percentage.

Figure 7 shows that CAS-024 acts synergystically with chemotherapeutic agents fludarabine and vincristine to kill mantle cell lymphoma (MCL) cells, Rec-1 cells.

Figure 8 is a bar graph showing the level of depletion of peripheral blood lymphocytes in human patients treated with an anti-CD37 SMIP molecule of this disclosure.

Figure 9 shows the lymphocyte depletion and course of treatment for patient BJB. BJB (part of Cohort 7) was treated with 3.0 mg/kg on days 1, 3 and 5 the first week followed by 3 weekly doses in the first cycle, and this same treatment was administered in a second cycle. Patient BJB showed a dramatic drop in lymphocytes (within 48 hrs), showed a decrease in palpable lymph nodes by day 4, and continues to respond to treatment.

Figure 10 shows the lymphocyte depletion and course of treatment for patient GRP. GRP (part of Cohort 4) was treated with 1.0 mg/kg once a week for four weeks as the first cycle, and then two months later was treated in the same way in a second cycle. Patient GRP showed a dramatic drop in lymphocytes (within 2 weeks), showed a 36% decrease in lymph node size by CT

scan, a decrease in spleen size, improved hemoglobin level, and continues to respond to treatment.

Figure 11 shows a combination index (CI) plot for inhibitory effects of CAS-024 and bendamustine against Rec-1 cell growth.

Figure 12 shows inhibitory effects of chlorambucil alone and in combination with CAS-024 on SU-DHL-6 cell growth.

Figure 13 shows a combination index plot for inhibitory effects of CAS-024 and chlorambucil on SU-DHL-6 cell growth.

Figure 14A shows tumor volume comparisons in tumor-bearing mice resulted from injections of DOHH2 cells and subsequently treated with huIgG (Human IgG, R&D Systems), CAS-024, bendamustine, and the combination of CAS-024 and bendamustine. Figure 14B shows tumor volume of individual mice on day 13 relative to day 0.

Figure 15 shows mean tumor volumes over time in tumor-bearing mice resulted from injections of DOHH2 cells and subsequently treated with huIgG, CAS-024, bendamustine, and the combination of CAS-024 and bendamustine. Values are the mean ± the standard error of the mean for each measurement day. Curves for each group end after one or more of the mice in the group were euthanized.

Figure 16 shows survival percentages over time of tumor-bearing mice resulted from injections of DOHH2 cells and subsequently treated with huIgG, CAS-024, bendamustine, and the combination of CAS-024 and bendamustine.

Figure 17 shows incidence of tumor free mice over time after treatments with huIgG, CAS-024, bendamustine, and the combination of CAS-024 and bendamustine.

DETAILED DESCRIPTION

In one aspect, the present disclosure provides the CD37-specific binding molecule CAS-024 (SEQ ID NO:253), which is a humanized version of CAS-006 (a small modular immunopharmaceutical (SMIP) protein having the immunoglobulin variable regions from mouse anti-human CD37 monoclonal

antibody G28-1). The CAS-024 SMIP protein is unexpectedly (1) expressed at up to about 25-fold higher levels than other humanized versions of CAS-006 (such as CAS-002, CAS-003; *see* Examples 2 and 5), (2) capable of binding CD37 as well as CAS-006 while other humanized versions do not (*see* Examples 4 and 5), and (3) produced as a homogenous population of molecules as compared the heterogenous nature of other humanized versions (*see* Example 3). Additionally, the instant disclosure provides the CD37-specific binding molecule CAS-024 (SEQ ID NO:253) for use in methods for reducing B-cells or treating disease associated with aberrant B-cell activity comprising administering to a subject in need thereof an effective amount of CAS-024 provided herein.

In another aspect, the present disclosure provides compositions and methods for the combined use of any CD37-specific binding molecule and bifunctional chemotherapeutics (such as bendamustine) to reduce B-cells or treat a disease associated with aberrant B-cell activity. A surprising result of this combination is that this combination of compounds acts synergistically and results in a substantially more effective therapeutic regimen.

Prior to setting forth this disclosure in more detail, it may be helpful to an understanding thereof to provide definitions of certain terms to be used herein. Additional definitions are set forth throughout this disclosure.

In the present description, any concentration range, percentage range, ratio range, or integer range is to be understood to include the value of any integer within the recited range and, when appropriate, fractions thereof (such as one tenth and one hundredth of an integer), unless otherwise indicated. Also, any number range recited herein relating to any physical feature, such as polymer subunits, size or thickness, are to be understood to include any integer within the recited range, unless otherwise indicated. As used herein, "about" or "consisting essentially of" mean ± 20% of the indicated range, value, or structure, unless otherwise indicated. It should be understood that the terms "a" and "an" as used herein refer to "one or more" of the enumerated components. The use of the alternative (e.g., "or") should be understood to mean either one, both, or any combination thereof of the alternatives. As used herein, the terms "include" and "comprise" are used synonymously. In addition, it should be understood that the

individual compounds, or groups of compounds, derived from the various combinations of the structures and substituents described herein, are disclosed by the present application to the same extent as if each compound or group of compounds was set forth individually. Thus, selection of particular structures or particular substituents is within the scope of the present disclosure.

A “binding domain” or “binding region” according to the present disclosure may be, for example, any protein, polypeptide, oligopeptide, or peptide that possesses the ability to specifically recognize and bind to a biological molecule (*e.g.*, CD37) or complex of more than one of the same or different molecule or assembly or aggregate, whether stable or transient. A binding region includes any naturally occurring, synthetic, semi-synthetic, or recombinantly produced binding partner for a biological molecule or other target of interest. A variety of assays are known for identifying binding domains of the present disclosure that specifically bind a particular target, including Western blot, ELISA, or Biacore analysis.

Binding domains and fusion proteins thereof of this disclosure can be capable of binding to a desired degree, including “specifically or selectively binding” a target while not significantly binding other components present in a test sample, if they bind a target molecule with an affinity or K_a (*i.e.*, an equilibrium association constant of a particular binding interaction with units of 1/M) of, for example, greater than or equal to about 10^5 M^{-1}, 10^6 M^{-1}, 10^7 M^{-1}, 10^8 M^{-1}, 10^9 M^{-1}, 10^{10} M^{-1}, 10^{11} M^{-1}, 10^{12} M^{-1}, or 10^{13} M^{-1}. “High affinity” binding domains refers to those binding domains with a K_a of at least 10^7 M^{-1}, at least 10^8 M^{-1}, at least 10^9 M^{-1}, at least 10^{10} M^{-1}, at least 10^{11} M^{-1}, at least 10^{12} M^{-1}, at least 10^{13} M^{-1}, or greater. “Low affinity” binding domains refers to those binding domains with a K_a of up to 5×10^7 M^{-1}, up to 10^7 M^{-1}, up to 10^6 M^{-1}, up to 10^5 M^{-1}, or less.

Alternatively, affinity may be defined as an equilibrium dissociation constant (K_d) of a particular binding interaction with units of M (*e.g.*, 10^{-5} M to 10^{-13} M). Affinities of binding domain polypeptides and fusion proteins according to the present disclosure can be readily determined using conventional techniques (*see*, *e.g.*, Scatchard *et al*. (1949) Ann. N.Y. Acad. Sci. 51:660; and U.S. Patent Nos. 5,283,173, 5,468,614, or the equivalent).

The term “CD37-specific binding molecules” refer to a protein, polypeptide, oligopeptide or peptide that specifically binds to CD37 with a Ka of at least about 10^6 M^{-1} (*e.g.*, at least about 10^7 M^{-1}, 10^8 M^{-1}, 10^9 M^{-1}, 10^{10} M^{-1}, 10^{11} M^{-1}, 10^{12} M^{-1}, or 10^{13} M^{-1}).

The term “CD37-specific binding domain” refers to a portion or a domain of a CD37-specific binding molecule responsible for the specific CD37 binding of the molecule. A CD37-specific binding domain itself (*i.e.*, without any other portion of the CD37-specific binding molecule) binds to CD37 with a Ka of at least about 10^6 M^{-1} (*e.g.*, at least about 10^7 M^{-1}, 10^8 M^{-1}, 10^9 M^{-1}, 10^{10} M^{-1}, 10^{11} M^{-1}, 10^{12} M^{-1}, or 10^{13} M^{-1}). A CD37-specific binding domain itself may be sufficient as a CD37-specific binding molecule. Exemplary CD37-specific binding domains include CD37-specific scFv and Fab fragments, which can be derived from anti-CD37 antibodies, such as monoclonal antibody G28-1.

Terms understood by those in the art as referring to antibody technology are each given the meaning acquired in the art, unless expressly defined herein. For example, the terms “V_L” and “V_H” refer to the variable binding region derived from an antibody light and heavy chain, respectively. The variable binding regions are made up of discrete, well-defined sub-regions known as “complementarity determining regions” (CDRs) and “framework regions” (FRs). The terms “C_L” and “C_H” refer to an “immunoglobulin constant region,” *i.e.*, a constant region derived from an antibody light or heavy chain, respectively, with the latter region understood to be further divisible into C_{H1}, C_{H2}, C_{H3} and C_{H4} constant region domains, depending on the antibody isotype (IgA, IgD, IgE, IgG, IgM) from which the region was derived. A portion of the constant region domains makes up the Fc region (the "fragment crystallizable" region), which contains domains responsible for the effector functions of an immunoglobulin, such as ADCC (antibody-dependent cell-mediated cytotoxicity), CDC (complement-dependent cytotoxicity) and complement fixation, binding to Fc receptors, greater half-life *in vivo* relative to a polypeptide lacking an Fc region, protein A binding, and perhaps even placental transfer (*see* Capon *et al*., Nature, 337:525 (1989)). Further, a polypeptide containing an Fc region allows for dimerization or multimerization of the polypeptide.

A "hinge region" is an amino acid sequence interposed between and connecting a CD37-specific binding domain and another region (*e.g.*, a CH2 region) in a fusion protein so that the fusion protein is still capable of specific binding to CD37 (*i.e.*, with a Ka of at least about 10^6 M^{-1}, 10^7 M^{-1}, 10^8 M^{-1}, 10^9 M^{-1}, 10^{10} M^{-1}, 10^{11} M^{-1}, 10^{12} M^{-1}, or 10^{13} M^{-1}). In certain embodiments, a hinge region is an immunoglobulin hinge region.

An "immunoglobulin hinge region" refers to a wild type immunoglobulin hinge region or an altered wild type immunoglobulin hinge region.

According to crystallographic studies, the immunoglobulin hinge region can be further subdivided functionally into three regions: the upper hinge region, the core region, and the lower hinge region. The upper hinge region includes amino acids from the carboxyl end of CH1 to the first residue in the hinge that restricts motion, generally the first cysteine residue that forms an interchain disulfide bond between the two heavy chains. The length of the upper hinge region correlates with the segmental flexibility of the antibody. The core hinge region contains the inter-heavy chain disulfide bridges, and the lower hinge region joins the amino terminal end of the CH2 domain and includes residues in CH2. *Id*. The core hinge region of human IgG1 contains the sequence Cys-Pro-Pro-Cys (SEQ ID NO:264) which, when dimerized by disulfide bond formation, results in a cyclic octapeptide believed to act as a pivot, thus conferring flexibility.

A "wild type immunoglobulin hinge region," as used herein refers to a naturally occurring amino acid sequence interposed between and connecting CH1 and CH2 regions of a single chain of an antibody. It contains the upper hinge region, the core hinge region, and the portion of the lower hinge region that is not part of CH2 region. An exemplary wild type immunoglobulin hinge region is human IgG1 hinge region as set forth in SEQ ID NO:90, in which from its amino terminus to its carboxyl terminus, the first ten amino acids (EPKSCDKTHT, SEQ ID NO:263) form the upper hinge region, the next four amino acids (CPPC, SEQ ID NO:264) form the core hinge region, and the last amino acid (*i.e.*, proline) is the first amino acid in the lower hinge region and is not part of CH2.

An “altered wild type immunoglobulin hinge region” or “altered immunoglobulin hinge region” refers to (a) a wild type immunoglobulin hinge region with up to 30% amino acid changes (*e.g.*, up to 25%, 20%, 15%, 10%, or 5% amino acid substitutions or deletions), (b) a portion of a wild type immunoglobulin hinge region that is at least 10 amino acids (*e.g.*, at least 12, 13, 14 or 15 amino acids) in length with up to 30% amino acid changes (*e.g.*, up to 25%, 20%, 15%, 10%, or 5% amino acid substitutions or deletions), or (c) a portion of a wild type immunoglobulin hinge region that comprises the core hinge region (which may be 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15, or at least 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 amino acids in length). When an altered wild type immunoglobulin hinge region is interposed between and connecting a CD37-specific binding domain and another region (*e.g.*, a CH2 region) in a fusion protein, it allows the fusion protein to specifically bind to CD37 (*i.e.*, with a Ka of at least about 10^6 M^{-1}, 10^7 M^{-1}, 10^8 M^{-1}, 10^9 M^{-1}, 10^{10} M^{-1}, 10^{11} M^{-1}, 10^{12} M^{-1}, or 10^{13} M^{-1}). In certain embodiments, one or more cysteine residues in a wild type immunoglobulin hinge region may be substituted by one or more other amino acid residues (*e.g.*, one or more serine residues). An altered immunoglobulin hinge region may alternatively or additionally have a proline residue of a wild type immunoglobulin hinge region substituted by another amino acid residue (*e.g.*, a serine residue).

A “linker” refers to an amino acid sequence that connects a heavy chain variable region and a light chain variable region together and provides a spacer function compatible with interaction of the two sub-binding domains so that the resulting polypeptide is capable of CD37-specific binding.

"Derivative" as used herein refers to a chemically or biologically modified version of a compound that is structurally similar to a parent compound and (actually or theoretically) derivable from that parent compound. Generally, a "derivative" differs from an "analogue" in that a parent compound may be the starting material to generate a "derivative," whereas the parent compound may not necessarily be used as the starting material to generate an "analogue." A derivative may have different chemical or physical properties from the parent compound. For example, a derivative may be more hydrophilic or it may be a

mutated sequence having altered reactivity (*e.g.*, a CDR having an amino acid change that alters its affinity for a target) as compared to the parent compound or sequence.

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

"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.

A "therapeutically effective amount (or dose)" or "effective amount (or dose)" of a specific binding molecule or compound 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. The invention specifically

contemplates that one or more specific binding molecules may be administered according to methods of the invention, each in an effective dose.

"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 or B-cell proliferation, 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 malignancy or 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.

Additional definitions are provided in the following detailed description of the present disclosure.

Humanized CD37-Specific Binding Molecules

In one aspect, the present disclosure provides humanized CD37-specific binding molecules. These molecules may be in any form that contains a humanized CD37-specific binding domain, including a humanized anti-CD37 antibody, an Fab fragment of a humanized anti-CD37 antibody, a humanized CD37-specific single chain Fv (scFv), a humanized CD37-specific SMIP protein, a humanized CD37-specific PIMS protein (a fusion protein comprising the components of SMIP in the reverse orientation), a humanized CD37-specific SCORPION protein, and other bi- or multi-specific binding proteins that comprise at least one humanized CD37-specific binding domain. Detailed description of SMIP proteins and methods for making the same may be found, for example, in U.S. Patent Publication Nos. 2003/0133939, 2003/0118592, and 2005/0136049 and WO 2005017148. Constructs and methods for making PIMS proteins are described in U.S. Application No. 12/168,875. Methods for making SCORPION proteins may be found, for example, in PCT Application Publication No. WO 2007/146968. Other exemplary multi-functional fusion proteins may be found, for example, in U.S. Patent Application Publication No. 2006/0051844 and U.S. Patent No. 7,166,707. Certain bi- or multi-specific binding proteins may

comprise a CD37-specific scFv and one or more other binding domains that are not derived from an immunoglobulin.

Humanized CD37-Specific Binding Domains

An exemplary "humanized CD37-specific binding domain" is an immunoglobulin variable region specific for CD37 that comprises at least one human framework region.

A "human framework region" refers to a wild type (*i.e.*, naturally occurring) framework region of a human immunoglobulin variable region, an altered framework region of a human immunoglobulin variable region with less than about 50% (*e.g.*, preferably less than about 45%, 40%, 30%, 25%, 20%, 15%, 10%, 5%, or 1%) of the amino acids in the region are deleted or substituted (*e.g.*, with one or more amino acid residues of a nonhuman immunoglobulin framework region at corresponding positions), or an altered framework region of a nonhuman immunoglobulin variable region with less than about 50% (*e.g.*, less than 45%, 40%, 30%, 25%, 20%, 15%, 10%, or 5%) of the amino acids in the region deleted or substituted (*e.g.*, at positions of exposed residues and/or with one or more amino acid residues of a human immunoglobulin framework region at corresponding positions) so that, in one aspect, immunogenicity is reduced.

In certain embodiments, a human framework region is a wild type framework region of a human immunoglobulin variable region. In certain other embodiments, a human framework region is an altered framework region of a human immunoglobulin variable region with amino acid deletions or substitutions at one, two, three, four or five positions. In yet certain other embodiments, a human framework region is an altered framework region of a non-human immunoglobulin variable region with amino acid deletions or substitutions at one, two, three, four or five positions.

In certain embodiments, a humanized CD37-specific binding domain comprises at least one, two, three, four, five, six, seven or eight human framework regions (FR) selected from human light chain FR1, human heavy chain FR1, human light chain FR2, human heavy chain FR2, human light chain

FR3, human heavy chain FR3, human light chain FR4, and human heavy chain FR4.

Exemplary human FRs are set forth in SEQ ID NOS:140-146 (human heavy chain FR1), SEQ ID NOS:147, 150 and 151 (human heavy chain FR2), SEQ ID NO:154-160 (human heavy chain FR3), SEQ ID NOS: 161-163, 168 and 169 (human heavy chain FR4), SEQ ID NOS:170-172, 175, and 177-181 (human light chain FR1), SEQ ID NOS:182, 184-188 and 191 (human light chain FR2), SEQ ID NOS:194-198, 203 and 205 (human light chain FR3), and SEQ ID NOS:206-210 (human light chain FR4). Additional exemplary human FR regions may be found in FR regions of the CD37-specific SMIP proteins provided herein, such as CAS-001, CAS-002, CAS-003, or CAS-024.

Human FRs that may be present in CD37-specific binding domains also include variants of the exemplary FRs provided herein in which one or two amino acids of the exemplary FRs have been substituted or deleted.

In certain embodiments, a humanized CD37-specific binding domain comprises (a) a humanized light chain variable region that comprises a human light chain FR1, a human light chain FR2, a human light chain FR3, and a human light chain FR4, and (b) a humanized heavy chain variable region that comprises a human heavy chain FR1, a human heavy chain FR2, a human heavy chain FR3, and a human heavy chain FR4.

CD37-sepcific binding domains provided herein also comprise one, two, three, four, five, or six CDRs. Such CDRs may be nonhuman CDRs or altered nonhuman CDRs selected from CDR1, CDR2 and CDR3 of the light chain and CDR1, CDR2 and CDR3 of the heavy chain. In certain embodiments, a CD37-specific binding domain comprises (a) a light chain variable region that comprises a light chain CDR1, a light chain CDR2, and a light chain CDR3, and (b) a heavy chain variable region that comprises a heavy chain CDR1, a heavy chain CDR2, and a heavy chain CDR3.

Exemplary CDRs include CDR1 of the light chain as set forth in SEQ ID NO:61 (RASENVYSYLA) or SEQ ID NO:62 (RTSENVYSYLA), CDR1 of the heavy chain as set forth in SEQ ID NO:63 (GYNMN), CDR2 of the light chain as set forth in SEQ ID NO:64 (FAKTLAE), CDR2 of the heavy chain as set forth

in SEQ ID NO:65 (NIDPYYGGTTYNRKFKG), CDR3 of the light chain as set forth in SEQ ID NO:66 (QHHSDNPWT), CDR3 of the heavy chain as set forth in SEQ ID NO:67 (SVGPFDY), CDR3 of the heavy chain as set forth in SEQ ID NO:68 (SVGPFDS), and CDR3 of the heavy chain as set forth in SEQ ID NO:69 (SVGPMDY). Preferred light chain CDR1 is SEQ ID NO:61 (RASENVYSYLA) and preferred heavy chain CDR3 include SEQ ID NO:68 (SVGPFDS) or SEQ ID NO:69 (SVGPMDY).

Additional exemplary CDRs include CDR1 of the light chain as set forth in SEQ ID NO:128 (RTSQNVYSYLA), 129 (RTSESVYSYLA), 130 (RASQSVYSYLA), 131 (RASQSVSSYLA) and 132 (RASQSVSYYLA), CDR1 of the heavy chain as set forth in SEQ ID NOS:133 (SYMNM) and 134 (SYWIG), CDR2 of the light chain as set forth in SEQ ID NOS:135 (AASSLQS), 136 (GASTRAT) and 137 (DASNRAT), CDR2 of the heavy chain as set forth in SEQ ID NOS:138 (IIYPGDSDTRYSPSFQG) and 139 (RIDPSDSYTNYSPSFQG), CDR3 of the light chain as set forth in SEQ ID NO:220 (QHHSDNPWT), and CDR3 of the heavy chain as set forth in SEQ ID NOS:211 (SVGPMDY), 212 (SVGPFDY), 213 (SVGPMDV), 214 (SVGPFDS), 215 (SVGPFDP), 216 (SVGPFQH), 217 (SVGPFDV), 218 (SVGPFDI) and 219 (SVGPFDL). Further exemplary CDRs include the CDRs in the CD37-specific SMIP proteins provided herein.

In certain embodiments, CD37-specific binding domains comprise a humanized light chain variable region that comprises from its amino terminus to carboxyl terminus: human light chain FR1, light chain CDR1, human light chain FR2, light chain CDR2, human light chain FR3, light chain CDR3, and human light chain FR4.

In certain embodiments, CD37-specific binding domains comprise a humanized light chain variable region that comprises from its amino terminus to carboxyl terminus: human light chain FR1, light chain CDR1 as set forth in SEQ ID NO:61 or 62, human light chain FR2, light chain CDR2 as set forth in SEQ ID NO:64, human light chain FR3, light chain CDR3 as set forth in SEQ ID NO:66, and human light chain FR4. In further embodiments, CD37-specific binding domains comprise, consist essentially of, or consist of a humanized light chain

variable region that comprises from its amino terminus to carboxyl terminus: human light chain FR1 as set forth in SEQ ID NO:171, light chain CDR1 as set forth in SEQ ID NO:61, human light chain FR2 as set forth in SEQ ID NO:182, light chain CDR2 as set forth in SEQ ID NO:64, human light chain FR3 as set forth in SEQ ID NO:195, light chain CDR3 as set forth in SEQ ID NO:66, and human light chain FR4 as set forth in SEQ ID NO:206. Additional exemplary humanized light chains are set forth in SEQ ID NOS:237-240 and include the light chains in humanized CD37-specific SMIP proteins provided herein.

In certain embodiments, CD37-specific binding domains comprise a humanized heavy chain variable region that comprises from its amino terminus to carboxyl terminus: human heavy chain FR1, heavy chain CDR1, human heavy chain FR2, heavy chain CDR2, human heavy chain FR3, heavy chain CDR3, and human heavy chain FR4.

In certain embodiments, CD37-specific binding domains comprise a humanized heavy chain variable region that comprises from its amino terminus to carboxyl terminus: human heavy chain FR1, heavy chain CDR1 as set forth in SEQ ID NO:63, human heavy chain FR2, heavy chain CDR2 as set forth in SEQ ID NO:65, human heavy chain FR3, heavy chain CDR3 as set forth in SEQ ID NO:67, 68 or 69, and human heavy chain FR4. In further embodiments, CD37-specific binding domains comprise consist essentially of, or consist of a humanized heavy chain variable region that comprises from its amino terminus to carboxyl terminus: human heavy chain FR1 as set forth in SEQ ID NO:144, heavy chain CDR1 as set forth in SEQ ID NO:63, human heavy chain FR2 as set forth in SEQ ID NO:151, heavy chain CDR2 as set forth in SEQ ID NO:65, human heavy chain FR3 as set forth in SEQ ID NO:158, heavy chain CDR3 as set forth in SEQ ID NO:67, 68 or 69, and human heavy chain FR4 as set forth in SEQ ID NO:161. Additional exemplary humanized light chains are set forth in SEQ ID NOS:242-245 and include the light chains in humanized CD37-specific SMIP proteins provided herein.

In certain embodiments, CD37-specific binding domains may be in the form of a Fab or scFv fragment. In a preferred embodiment, the CD37-specific binding domain is a humanized CD37-specific scFv that comprises a light

chain variable region and a heavy chain variable region joined together via a linker. In further embodiments, both the light and heavy chain variable regions are humanized, and may comprise both a humanized light chain variable region as set forth in SEQ ID NO:238 and a humanized heavy chain variable region as set forth in SEQ ID NO:245.

In still further embodiments, only the light or heavy chain variable region is humanized. For example, CD37-specific binding domains may comprise a humanized light chain variable region (*i.e.*, a light chain variable region that comprises at least one human FR) and a nonhuman heavy chain variable chain region (*e.g.*, mouse or rat). Alternatively, CD37-specific binding domains may comprise a nonhuman light chain variable region (*e.g.*, mouse or rat) and a humanized heavy chain variable chain region (*i.e.*, a heavy chain variable region that comprises at least one human FR). Both types of CD37-specific binding domains may be referred to as a "hybrid human-nonhuman CD37-specific binding domain" or as a “chimeric CD37-specific binding domains.”

In certain embodiments, the carboxyl terminus of the light chain variable region in a humanized CD37-specific scFv is linked to the amino terminus of the heavy chain variable region via a linker. Thus, the resulting scFv has from its amino terminus to its carboxyl terminus: the light chain variable region, the linker, and the heavy chain variable region. In certain other embodiments, the carboxyl terminus of the heavy chain variable region in a humanized CD37-specific scFv is linked to the amino terminus of the light chain variable region via a linker. Thus, the resulting scFv has from its amino terminus to its carboxyl terminus: the heavy chain variable region, the linker, and the heavy chain variable region.

In certain embodiments, the linkers have 5-30 amino acids, such as 15-25 amino acids. In certain embodiments, the linkers comprises $(Gly_nSer)_m$, wherein n and m may be an integer independently selected from 1 to 5. For example, in certain embodiments, n is 4, and m is 1, 2, 3, 4 or 5. In certain embodiments, one or two amino acids other than Gly or Ser may be present at the amino terminus, carboxyl terminus or both termini. In certain other embodiments, one or two amino acids other than Gly or Ser may be used to

substitute a Gly or Ser in a linker that comprises $(Gly_nSer)_m$ with m and n as defined above. An exemplary linker has the sequence $(Gly_4S)_5$ as set forth in SEQ ID NO:229. Additional exemplary linker sequences are set forth in SEQ ID NOS:225-228.

In certain embodiments, humanized CD37-specific binding domains or CD37-specific binding molecules competes with G28-1 mAb for binding to CD37. In other words, in such embodiments, CD37 binding of G28-1 mAb is reduced in the presence of other CD37-specific binding domains (such as anti-CD37 monoclonal antibodies) or CD37-specific binding molecules compared to CD37 binding of G28-1 mAb in the absence of CD37-specific binding domains or CD37-specific binding molecules. Competitive binding assays are known in the art, such as those described in the Examples 4-6, and may be used to determine whether a given CD37-specific binding domain or CD37-specific binding molecule is capable of competing with G28-1 mAb for binding to CD37.

Humanized CD37-Specific SMIP Polypeptides

In certain embodiments, CD37-specific binding molecules are CD37-specific small modular immunopharmaceutical (SMIP) polypeptides. SMIP proteins are binding domain-immunoglobulin fusion proteins that typically comprise from their amino termini to carboxyl termini: a binding domain derived from an immunoglobulin (*e.g.*, a scFv), a hinge region, and an effector domain (*e.g.*, IgG CH2 and CH3 regions). In preferred embodiments, the CD37-specific binding SMIP polypeptides are humanized.

The hinge region of a humanized CD37-specific binding SMIP polypeptide may be an immunoglobulin hinge region. In certain embodiments, the hinge region is a wild type immunoglobulin hinge region, such as an IgG hinge, IgA hinge, IgD hinge, IgE hinge or a fragment thereof (*e.g.*, 4 to 20 or 5 to 15 amino acids in length) that comprises a core hinge region. In certain preferred embodiments, a hinge region may be an antibody hinge region selected from human IgG1, human IgG2, human IgG3, human IgG4, or fragments or variants thereof. In some embodiments, the hinge region is a wild type immunoglobulin hinge region or portion thereof, such as a human immunoglobulin hinge region.

Exemplary hinges for such embodiments are wild type human IgG1 hinge region as set forth in SEQ ID NO:90, wild type human IgA1 hinge as set forth in SEQ ID NO:115, wild type human IgA2 hinge as set forth in SEQ ID NO:116, wild type human IgG3 hinge as set forth in SEQ ID NO:118, a portion of human IgG3 hinge as set forth in SEQ ID NO:258, and human IgD hinge as set forth in SEQ ID NO:127. In certain embodiments, one or more amino acid residues may be added at the amino- or carboxy- terminus of a wild type immunoglobulin hinge region as part of fusion protein construct design. Such amino acid residues are referred to as "junction amino acids" (*see* Table 4).

In certain embodiments, the hinge region is an altered (mutated) wild type immunoglobulin hinge region, such as an altered wild type IgG immunoglobulin hinge region, or an altered portion of a wild type immunoglobulin hinge region. For example, the wild type human IgG1 hinge region contains three cysteine residues – the most N-terminal cysteine is referred to the first cysteine, whereas the most C-terminal cysteine in the hinge region is the third cysteine. In certain embodiments, the mutated human IgG1 hinge region has only two cysteine residues, such as a human IgG1 hinge region with the first cysteine substituted by a serine. In certain other embodiments, the mutated human IgG1 hinge region has only one cysteine residue. In certain embodiments, the proline C-terminal to the third cysteine in the human IgG1 hinge region is substituted, for example, by a serine. Exemplary mutated human IgG1 hinge regions are as set forth in SEQ ID NOS:92, 94, 102, 104, 255, 256, 106, 108, 257, 96, 110, 112, 98, and 100. Exemplary mutated portions of human IgG3 hinge regions are as set forth in SEQ ID NOS:120, 126, 259-261, 122, and 124. In certain embodiments, one or more amino acid residues may be added at the amino-or carboxy-terminus of a mutated immunoglobulin hinge region as part of fusion protein construct design. Examples of such modified hinge regions are indicated in italics in SEQ ID NOS:231-235.

In certain embodiments, a hinge region comprises or has a sequence that is at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least

96%, at least 97%, at least 98%, at least 99% identical to a wild type immunoglobulin hinge region, such as a wild type human IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD and IgE hinges.

In further embodiments, altered hinge regions can be based on a wild type immunoglobulin hinge region (*e.g.*, an IgG1 hinge region) and contain one or more (*e.g.*, 1, 2, 3, or 4) insertions, one or more (*e.g.*, 1, 2, 3, or 4) deletions, one or more (*e.g.*, 1, 2, 3, or 4) amino acid substitutions (*e.g.*, conservative amino acid substitutions or non-conservative amino acid substitutions), or a combination of the above-noted mutations, when compared with the wild type immunoglobulin hinge region, but provided that the modified hinge retains the flexibility or rigidity suitable for properly orienting the binding domain of a fusion binding protein to interact with its target. The insertion(s), deletion(s) or substitution(s) may be anywhere in the wild type immunoglobulin hinge region, including at the amino- or carboxy-terminus or both.

As described herein, CD37-specific SMIP polypeptides may comprise an immunoglobulin C_{H2} region. In certain embodiments, the immunoglobulin C_{H2} region is a wild type immunoglobulin C_{H2} region, such as a wild type human immunoglobulin C_{H2} region, including wild type human IgA1, IgA2, IgD, IgE, IgG1, IgG2, IgG3, IgG4 and IgM C_{H2} regions. In certain embodiments, the immunoglobulin C_{H2} region is a human IgG1 C_{H2} region.

In certain other embodiments, the immunoglobulin C_{H2} region is an altered wild type immunoglobulin C_{H2} region. For example, the altered wild type immunoglobulin C_{H2} region may be a human IgG1 C_{H2} region but with one, two, three, four or five mutations at positions 234 to 238, 253, 279, 310, 318, 320, 322, and 331 (EU numbering, Ward *et al*., 1995 *Therap. Immunol.* 2:77-94). The mutations in such positions reduce or eliminate the antibody-dependent cell-mediated cytotoxicity (ADCC) activity, Fc receptor-binding capability, and/or complement fixation.

As described herein, a humanized CD37-specific SMIP polypeptides may comprise an immunoglobulin C_{H3} region. In certain embodiments, an immunoglobulin C_{H3} region polypeptide is a wild type immunoglobulin C_{H3} region polypeptide, including a wild type C_{H3} region of any

one of the various immunoglobulin isotypes (*e.g.*, IgA, IgD, IgG1, IgG2, IgG3, IgG4, IgE, or IgM) from various species (*i.e.*, human, mouse, rat or other mammals). In other embodiments, an immunoglobulin C_{H3} region polypeptide is a mutated immunoglobulin C_{H3} region polypeptide. The mutations in the immunoglobulin C_{H3} region may be at one or more positions that are involved in complement fixation, such as at H433 or N434.

In certain embodiments, a humanized CD37-specific SMIP polypeptides may contain one or more additional regions. Such additional regions may be a leader sequence at the amino-terminus for secretion of an expressed SMIP polypeptide, an additional Fc sub-region (*e.g.*, a wild type or mutated C_{H4} region of IgM or IgE), a tail sequence at its carboxy-terminus for identification or purification purposes (*e.g.*, epitope tags for detection or purification, including a 6-Histidine tag or a FLAG epitope), or additional amino acid residues that arise from use of specific expression systems. Exemplary leader peptides of this disclosure include natural leader sequences or others, such as those as set forth in SEQ ID NOS:223 and 224.

This disclosure includes CD37-specific SMIP polypeptides that exhibit at least 80 percent identity (*e.g.*, 82%, 84%, 85%, 86%, 88%, 90%, 92%, 94%, 95%, 96%, 97%, 98% or 99%) to the polypeptide set forth in SEQ ID NO:2, wherein the CD37-specific SMIP polypeptide binds CD37. In further embodiments, such polypeptides having at least 80% identity with SEQ ID NO:2 may be further humanized. Exemplary humanized CD37-specific SMIP polypeptides comprise, consist essential of, or consist of 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, 52, 80, 82, 84, 86, 88, and 222 in which the leader sequences are deleted, as well as SEQ ID NOS:247-254 and 266-269.

"Sequence identity," as used herein, refers to the percentage of amino acid residues in one sequence that are identical with the amino acid residues in another reference polypeptide sequence after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the

sequence identity. The percentage sequence identity values are generated by the NCBI BLAST2.0 software as defined by Altschul *et al*. (1997) "Gapped BLAST and PSI-BLAST: a new generation of protein database search programs", Nucleic Acids Res. 25:3389-3402, with the parameters set to default values.

In a preferred embodiment, the present disclosure provides a humanized CD37-specific SMIP polypeptide that comprises from amino terminus to carboxyl terminus: a humanized heavy chain variable region (V_H), a $(G_4S)_5$ linker (SEQ ID NO:229), a humanized light chain variable region (V_L), an altered IgG1 hinge, a human IgG1 CH2 region, and a human IgG1 CH3 region. The humanized heavy chain variable region comprises from its amino terminus to its carboxyl terminus: a human heavy chain FR1, a heavy chain CDR1 as set forth in SEQ ID NO:63, a human heavy chain FR2, a CDR2 as set forth in SEQ ID NO:65, a human heavy chain FR3, CDR3 as set forth in SEQ ID NO:67, 68 or 69, and a human heavy chain FR4. The humanized light chain variable region comprises from its amino terminus to its carboxyl terminus: a human light chain FR1, a light chain CDR1 as set forth in SEQ ID NO:61 or 62, a human light chain FR2, a light chain CDR2 as set forth in SEQ ID NO:64, a human light chain FR3, and a light chain CDR3 as set forth in SEQ ID NO:66, and a human light chain FR4.

In some of the above preferred embodiments, the human heavy chain FR1, FR2, and FR3 comprise SEQ ID NOS:144, 151, and 158, respectively, and the heavy chain FR4 comprises SEQ ID NO:161 or 162. In further preferred embodiments, the human light chain FR1, FR2, FR3, and FR4 comprise SEQ ID NOS:171, 182, 195, and 206, respectively. Alternatively, both the heavy and light chains contain these sequences.

The CAS-024 SMIP protein is unexpectedly (1) expressed at up to about 25-fold higher levels than other humanized versions of CAS-006 (such as CAS-002, CAS-003; *see* Examples 2 and 5), (2) capable of binding CD37 as well as CAS-006 while other humanized versions do not (*see* Examples 4 and 5), and (3) produced as a homogenous population of molecules as compared the heterogenous nature of other humanized versions (*see* Example 3) In a preferred embodiment, the instant disclosure provides a CD37-specific binding protein that

comprises or consists of CAS-024 (SEQ ID NO:253). In particular, this humanized CD37-specific binding molecule has substantially the same CD37 binding affinity as its parent chimeric molecule (CAS-006, SMIP protein having the immunoglobulin variable regions from mouse anti-human CD37 monoclonal antibody G28-1) in contrast to other humanized molecules, is expressed at high levels compared to other humanized molecules, and/or shows a high degree of homogeneity when purified, for example, via size exclusion chromatography (SEC) in contrast to other humanized molecules. In addition, this CAS-024 CD37-specific binding molecule has been shown to be effective in inhibiting tumor growth and causing long term tumor regression.

The disclosure also includes an isolated nucleic acid molecule comprising a nucleotide sequence encoding humanized CD37-specific binding molecules and the components thereof, including human or humanized FRs, CDRs, humanized light chain variable regions, humanized heavy chain variable regions, humanized scFv, and humanized SMIP polypeptides. Exemplary isolated nucleic acid molecules that encode humanized CD37-specific SMIP polypeptides include those that comprise 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, 51, 79, 81, 83, 85, 87, and 221. In one embodiment, the disclosure includes vectors that comprise these nucleic acid molecules and host cells that comprise the vectors.

The disclosure 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.

Compounds Useful for Combination Therapy

The present disclosure also provides a combination therapy using any of the CD37-specific binding molecules known in the art or disclosed herein and bifunctional chemotherapeutics (*e.g.*, bendamustine).

The CD37-specific binding molecules useful for the combination therapy may be in any forms that contain a CD37-specific binding domain, including an anti-CD37 antibody, an Fab fragment of anti-CD37 antibody, a

CD37-specific single chain Fv (scFv), a CD37-specific SMIP, a CD37-specific PIMS, a CD37-specific SCORPION, and other bi- or multi-specific binding proteins that comprise at least one CD37-specific binding protein.

In certain embodiments, the CD37-specific binding molecules useful for combination therapy with a bifunctional chemotherapeutic are CD37-specific antibodies. Such antibodies include those used for characterizing the CD37 antigen in the Thrid HLDA Workshop, *i.e.*, HD28, G28-1, HH1, Bl14, 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 useful for the combination therapy 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), stating that all these antibodies recognize only one CD37 epitope, and Schwartz-Albiez *et al*., 14: 905-914 (1988), indicating that the epitope is situated in the carbohydrate moiety of CD37). Another CD37-specific antibody that may be used in combination therapy is S-B3 (Biosys).

In certain embodiments, the CD37-specific binding molecules useful for combination therapy with a bifunctional chemotherapeutic are CD37-specific SMIP polypeptides. An exemplary SMIP polypeptide comprises SEQ ID NO:2. Additional exemplary SMIP polypeptides include those described in WO 2005017148, such as (1) G28-1 scFv (SSS-S) H WCH2 WCH3 comprising a G28-1 scFv, an altered human IgG1 hinge in which all three cysteine residues and a proline carboxyl terminus to the third cysteine in a human IgG1 hinge region are mutated to serine residues, and wild type human IgG1 CH2 and CH3 domains; (2) G28-1 scFv IgAH WCH2 WCH3 comprising a G28-1 scFv, a portion of human IgA hinge, and human IgG1 CH2 and CH3 domains; (3) G28-1 scFv VHL11S (SSS-S) H WCH2 CH3 comprising a G28-1 scFv, an altered human IgG1 hinge in which all three cysteine residues and a proline carboxyl terminus to the third cysteine in the hinge region are mutated to serine residues, and human IgG1 CH2 and CH3 domains, wherein the leucine at position 11 of the heavy chain variable region is substituted with a serine; (4) G28-1 scFv VH L11S (CSS-S) H WCH2 CH3 comprising a G28-1 scFv, an altered human IgG1 hinge in

which the cysteine residues at the second and third positions and a proline carboxyl terminus to the third cysteine are substituted with serine residues, and human IgG1 CH2 and CH3 domains, wherein the leucine at position 11 of the heavy chain variable region is substituted with a serine; (5) G28-1 scFv VHL11S (CSC-S) H WCH2 CH3 comprising a G28-1 scFv, an altered human IgG1 hinge in which the cysteine residue at the second position and a proline carboxyl terminus to the cysteine at the third position were substituted with serine residues, and human IgG1 CH2 and CH3 domains, wherein the leucine at position 11 of the heavy chain variable region is substituted with a serine; (6) G28-1 scFv VH11S (SSC-P) H WCH2 WCH3 comprising a G28-1 scFv, an altered human IgG1 hinge in which the first and second cysteine residues in the hinge region are mutated to serine residues, and human IgG1 CH2 and CH3 domains, wherein the leucine at position 11 of the heavy chain variable region is substituted with a serine; (7) G28-1 scFv VH11S (SCS-S) H WCH2 WCH3 comprising a G28-1 scFv, an altered human IgG1 hinge in which the first and third cysteine residues and a proline carboxyl terminus to the third cysteine in the hinge regions are mutated to serine residues, and human IgG1 CH2 and CH3 domains, wherein the leucine at position 11 of the heavy chain variable region is substituted with a serine; (8) G28-1 scFv VHL11S (CCS-P) H WCH2 WCH3 comprising a G28-1 scFv, an altered human IgG1 hinge in which the third cysteine residue in the hinge region is substituted with a serine, and human IgG1 CH2 and CH3 domains, wherein the leucine at position 11 of the heavy chain variable region is substituted with a serine (9) G28-1scFv VHL11S (SCC-P) H WCH2 WCH3 comprising a G28-1 scFv, an altered human IgG1 hinge in which the first cysteine is substituted with a serine, and human CH2 and CH3 domains, wherein the leucine at position 11 of the heavy chain variable region is substituted with a serine; (10) G28-1 scFv VH L11S mIgE CH2 CH3 CH4, comprising a G28-1 scFv and mouse IgE CH2, CH3 and CH4 regions, wherein the leucine at position 11 of the heavy chain variable region is substituted with a serine; (11) G28-1 scFv VH L11S mIgA WIgACH2 T4CH3, comprising a G28-1 scFv, a mouse IgA hinge, and a wild type IgA CH2 and a truncated IgA CH3 domain lacking the 4 carboxy amino acids GTCY (SEQ ID NO:265); (12) G28-1

scFv VHL11S hIgE CH2 CH3 CH4, comprising a G28-1 scFv and human IgE CH2, CH3 and CH4 regions, wherein the leucine at position 11 of the heavy chain variable region is substituted with a serine; and (13) G28-1 scFv VHL11S hIgAH WIgACH2 TCH3 comprising a G28-1 scFv, a portion of human IgA hinge, a wild type IgA CH2 and a truncated IgA CH3 domain lacking the 4 carboxy amino acids GTCY (SEQ ID NO:265), wherein the leucine at position 11 of the heavy chain variable region is substituted with a serine.

In certain embodiments, CD37-specific binding molecules useful for combination therapy with a bifunctional chemotherapeutic are humanized CD37-specific binding molecules described herein, including humanized anti-CD37 antibodies, Fab fragments of humanized anti-CD37 antibody, humanized CD37-specific PIMS protein, humanized CD37-specific SCORPION protein, and other bi- or multi-specific binding proteins that comprise at least one humanized CD37-specific binding protein, especially humanized CD37-specific single chain Fv (scFv) and humanized CD37-specific SMIP polypeptides.

Certain CD37-specific binding molecules contemplated in this disclosure have affinities for CD37 of about 0.5 to about 10 nM. Another characteristic of certain CD37-binding molecules contemplated in this disclosure is that they exhibit a half life in circulation of about 5 to about 30 days.

In certain embodiments, CD37-specific binding molecules are capable of competing with G28-1 mAb in CD37-specific binding.

Bendamustine (4-[5-[Bis(2-chloroethyl)amino]-1-methylbenzimidazol-2-yl]butanoic acid) is a nitrogen mustard with alkylator and antimetabolite activities. Bendamustine has both an alkylating group and a benzimidazole ring. The alkylating group allows bendamustine metabolites to alkylate and crosslink macromolecules, resulting in DNA, RNA and protein synthesis inhibition, and subsequently apoptosis. The benzimidazole ring may allow bendamustine to act as a purine analogue. Bendamustine hydrochloride has trade names TREANDA® and RIBOMUSTIN®.

Although bendamustine or its salts are preferred therapeutic agents that may be used in combination with CD37-specific binding molecules, other therapeutic agents that both comprise one or more alkylating groups and are

capable of functioning as a purine analogue may also be used in combination with CD37-sepcific binding molecules according to the present disclosure.

The term “alkylating group,” as used herein, refers to a group that enables the compound comprising this group to attach an alkyl group to DNA. The compound that comprises an alkylating group may be referred to as an “alkylating agent.” In certain embodiments, alkylating agents are nitrogen mustards.

The term “purine analogue” refers to an antimetabolite that mimics the structure of metabolic purines (*e.g.*, adenine and guanine) and has one, two, three or four substituents at the purine ring that differ from metabolic purines. Exemplary purine analogues include azathioprine, mercaptopurine, thioguanine, fludarabine, pentostatin and cladribine.

A therapeutic agent is “capable of functioning as a purine analogue” if it possesses at least one function of a purine analogue. Exemplary functions of purine analogues include interference with or inhibition of purine nucleotide synthesis, purine nucleotide metabolism, nucleic acid synthesis, nucleic acid processing, or nucleic acid function, such as inhibiting ribonucleotide reductase, DNA polymerase, adenosine deaminase, and being incorporated into DNA or RNA.

Compositions and Methods

In one aspect, the present disclosure provides a method for reducing B cells or treating a disease associated with aberrant B cell activity comprising administering to a subject in need thereof (*i.e.*, an individual having or suspected of having a disease associated with aberrant B-cell activity) an effective amount of a humanized CD37-specific binding molecule provided herein (*e.g.*, CAS-024).

In another aspect, the present disclosure provides a method for reducing B cells or treating a disease associated with aberrant B cell activity comprising administering to a subject in need thereof an effective amount of a CD37-specific binding molecule (*e.g.*, CAS-024) and a bifunctional chemotherapeutic (*e.g.*, bendamustine). As described above, CD37-specific

binding molecules useful for combination therapy with a bifunctional chemotherapeutic are not limited to humanized CD37-specific binding molecules, but include other CD37-specific binding molecules that have not been humanized.

In one embodiment, a composition comprising a CD37 therapeutic and a bifunctional chemotherapeutic act synergistically in reducing B cells or treating a disease associated with aberrant B cell activity. Two or more compounds that act synergistically interact such that the combined effect of the compounds is greater than the sum of the individual effects of each compound when administered alone (*see*, *e.g.*, Berenbaum, Pharmacol. Rev. 41:93, 1989). For example, an interaction between small modular immunopharmaceutical that targets CD37 and another agent or compound may be analyzed by a variety of mechanistic and empirical models (*see*, *e.g.*, Ouzounov et al., Antivir. Res. 55:425, 2002). A commonly used approach for analyzing the interaction between a combination of agents employs the construction of isoboles (iso-effect curves, also referred to as isobolograms), in which the combination of agents (d_a, d_b) is represented by a point on a graph, the axes of which are the dose-axes of the individual agents (*see*, *e.g.*, Ouzounov *et al.*, supra; *see also* Tallarida, J. Pharmacol. Exp. Therap. 298:865, 2001).

Another method for analyzing drug-drug interactions (antagonism, additivity, synergism) known in the art includes determination of combination indices (CI) according to the median effect principle to provide estimates of IC_{50} values of compounds administered alone and in combination (*see*, *e.g.*, Chou. In Synergism and Antagonism Chemotherapy. Eds. Chou and Rideout. Academic Press, San Diego Calif., pages 61-102, 1991; CalcuSyn™ software). A CI value of less than one represents synergistic activity, equal to one represents additive activity, and greater than one represents antagonism.

Still another exemplary method is the independent effect method (Pritchard and Shipman, Antiviral Res. 14:181, 1990; Pritchard and Shipman, Antiviral Therapy 1:9, 1996; MACSYNERGY™ II software, University of Michigan, Ann Arbor, Mich.). MACSYNERGY ™ II software allows a three-dimensional (3-D) examination of compound interactions by comparing a calculated additive

surface to observed data to generate differential plots that reveal regions (in the form of a volume) of statistically greater than expected (synergy) or less than expected (antagonism) compound interactions. For example, a composition comprising a CD37-specific binding molecule and a bifunctional chemotherapeutic alters viral replication will be considered to have synergistic activity or have a synergistic effect when the volume of synergy produced as calculated by the volume of the synergy peaks is preferably about 15% greater than the additive effect (that is, the effect of each agent alone added together), or preferably about a 2-fold to 10-fold greater than the additive effect, or preferably about a 3-fold to 5-fold or more greater than the additive effect.

In further embodiments, a CD37-specific binding molecule and a bifunctional chemotherapeutic can be administered to act synergistically in the treatment of B-cell malignancies or B-cell cancers. B-cell malignancies or 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.

Burkitt's lymphoma (or "Burkitt's B cell malignancy", or "Burkitt's tumor", or "Malignant lymphoma, Burkitt's type") is a cancer of the lymphatic system (in particular, B lymphocytes). It can be divided into three main clinical variants: the endemic, the sporadic and the immunodeficiency-associated variants.

Non-Burkitt's B cell malignancies include, but are not limited to, B-cell chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma, B-cell prolymphocytic leukemia, an acute lymphoblastic leukemia (ALL), lymphoplasmacytic lymphoma (including, but not limited to, Waldenstrom's macroglobulinemia), marginal zone lymphomas (including, but not limited to, splenic marginal zone B-cell lymphoma, nodal marginal zone lymphoma, and extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) type), hairy cell leukemia, plasma cell myeloma/plasmacytoma, follicular lymphoma, mantle cell lymphoma (MCL), diffuse large cell B-cell lymphoma, transforming large B cell lymphoma, mediastinal large B-cell lymphoma, intravascular large B-cell lymphoma, primary effusion lymphoma, and non-Burkitt's non-Hodgkins lymphoma (NHL).

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, toxic epidermal necrolysis, systemic scleroderma and sclerosis, CREST syndrome, responses associated with inflammatory bowel disease, Crohn's disease, ulcerative colitis, respiratory distress syndrome, adult respiratory distress syndrome (ARDS), meningitis, encephalitis, uveitis, colitis, glomerulonephritis, allergic conditions, eczema, asthma, conditions involving infiltration of T cells and chronic inflammatory responses, atherosclerosis, autoimmune myocarditis, leukocyte adhesion deficiency, systemic lupus erythematosus (SLE), subacute cutaneous lupus erythematosus, discoid lupus, lupus myelitis, lupus cerebritis, juvenile onset diabetes, multiple sclerosis, allergic encephalomyelitis, neuromyelitis optica, rheumatic fever, Sydenham's chorea, immune responses associated with acute and delayed hypersensitivity mediated by cytokines and T-lymphocytes, tuberculosis, sarcoidosis, granulomatosis including Wegener's granulomatosis and Churg-Strauss disease, agranulocytosis, vasculitis (including hypersensitivity vasculitis/angiitis, ANCA and rheumatoid vasculitis), aplastic anemia, Diamond Blackfan anemia, immune

hemolytic anemia including autoimmune hemolytic anemia (AIHA), pernicious anemia, pure red cell aplasia (PRCA), Factor VIII deficiency, hemophilia A, autoimmune neutropenia, pancytopenia, leukopenia, diseases involving leukocyte diapedesis, central nervous system (CNS) inflammatory disorders, multiple organ injury syndrome, myasthenia gravis, antigen-antibody complex mediated diseases, anti-glomerular basement membrane disease, anti-phospholipid antibody syndrome, allergic neuritis, Behcet disease, Castleman's syndrome, Goodpasture's syndrome, Lambert-Eaton Myasthenic Syndrome, Reynaud's syndrome, Sjorgen's syndrome, Stevens-Johnson syndrome, solid organ transplant rejection, graft versus host disease (GVHD), pemphigoid bullous, pemphigus, autoimmune polyendocrinopathies, seronegative spondyloarthropathies, Reiter's disease, stiff-man syndrome, giant cell arteritis, immune complex nephritis, IgA nephropathy, IgM polyneuropathies or IgM mediated neuropathy, idiopathic thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP), Henoch-Schonlein purpura, autoimmune thrombocytopenia, autoimmune disease of the testis and ovary including autoimmune orchitis and oophoritis, primary hypothyroidism; autoimmune endocrine diseases including autoimmune thyroiditis, chronic thyroiditis (Hashimoto's Thyroiditis), subacute thyroiditis, idiopathic hypothyroidism, Addison's disease, Grave's disease, autoimmune polyglandular syndromes (or polyglandular endocrinopathy syndromes), Type I diabetes also referred to as insulin-dependent diabetes mellitus (IDDM) and Sheehan's syndrome; autoimmune hepatitis, lymphoid interstitial pneumonitis (HIV), bronchiolitis obliterans (non-transplant) vs NSIP, Guillain-Barre' Syndrome, large vessel vasculitis (including polymyalgia rheumatica and giant cell (Takayasu's) arteritis), medium vessel vasculitis (including Kawasaki's disease and polyarteritis nodosa), polyarteritis nodosa (PAN) ankylosing spondylitis, Berger's disease (IgA nephropathy), rapidly progressive glomerulonephritis, primary biliary cirrhosis, Celiac sprue (gluten enteropathy), cryoglobulinemia, cryoglobulinemia associated with hepatitis, amyotrophic lateral sclerosis (ALS), coronary artery disease, familial Mediterranean fever, microscopic polyangiitis, Cogan's syndrome, Whiskott-Aldrich syndrome and thromboangiitis obliterans, autoimmune thyroid

disease (such as Graves' disease and Hashimoto's thyroiditis), Sjogren's syndrome, and idiopathic inflammatory myopathy (IIM), including dermatomyositis (DM) and polymyositis (PM). The above autoimmune diseases may also be treated with humanized CD37-specific binding molecules or with the combination of CD37-specific binding molecules and a bifunctional chemotherapeutic.

In one aspect of the disclosure, a humanized CD37-specific binding molecule or a combination of a CD37-specific binding molecule with a bifunctional chemotherapeutic is administered in a pharmaceutical composition. To administer a humanized CD37-specific binding molecule or a combination of a CD37-specific binding molecule with a bifunctional chemotherapeutic to human or test animals, it is preferable to formulate the binding molecule or the combination 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. In addition, compounds may form solvates with water or common organic solvents. Such solvates are contemplated as well.

Pharmaceutical compositions of the present disclosure containing a humanized CD37-specific binding molecule or a combination of a CD37-specific binding molecule with a bifunctional chemotherapeutic used in a method of the disclosure 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 of the present disclosure.

Formulation of the pharmaceutical composition will vary according to the route of administration selected (e.g., solution, emulsion). An appropriate composition comprising the antibody to be administered can be prepared in a physiologically acceptable vehicle or carrier. For solutions or emulsions, suitable carriers include, for example, aqueous or alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles can include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's or fixed oils. Intravenous vehicles can include various additives, preservatives, or fluid, nutrient or electrolyte replenishers

A variety of aqueous carriers, e.g., water, buffered water, 0.4% saline, 0.3% glycine, or aqueous suspensions may contain the active compound in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyl-eneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate.

A CD37-specific binding molecule, a combination of a CD37-specific binding molecule with a bifunctional chemotherapeutic, or a composition comprising the binding molecule or the combination can be lyophilized for storage

and reconstituted in a suitable carrier prior to use. This technique has been shown to be effective with conventional immunoglobulins. Any suitable lyophilization and reconstitution techniques can be employed. It will be appreciated by those skilled in the art that lyophilization and reconstitution can lead to varying degrees of activity loss and that use levels may have to be adjusted to compensate.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active compound in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above.

The concentration of CD37-specific binding molecule or bifunctional chemotherapeutic in these formulations can vary widely, for example from less than about 0.5%, usually at or at least about 1% to as much as 15 or 20% by weight and will be selected primarily based on fluid volumes, viscosities, *etc*., in accordance with the particular mode of administration selected. Thus, a typical pharmaceutical composition for parenteral injection could be made up to contain 1 mL sterile buffered water, and 50 mg of antibody. A typical composition for intravenous infusion could be made up to contain 250 mL of sterile Ringer's solution, and 150 mg of antibody. Actual methods for preparing parenterally administrable compositions will be known or apparent to those skilled in the art and are described in more detail in, for example, Remington's Pharmaceutical Science, 15th ed., Mack Publishing Company, Easton, Pa. (1980). An effective dosage of CD37-specific binding molecules (including humanized CD37-specific binding molecules) is within the range of 0.01 mg to 1000 mg per kg of body weight per administration.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous, oleaginous suspension, dispersions or sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. The suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution

or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, vegetable oils, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The prevention of the action of microorganisms can be brought about by various antibacterial or antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, or the like. In many cases, it will be desirable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Compositions useful for administration may be formulated with uptake or absorption enhancers to increase their efficacy. Such enhancers include for example, salicylate, glycocholate/linoleate, glycholate, aprotinin, bacitracin, SDS, caprate and the like. See, e.g., Fix (J. Pharm. Sci., 85:1282-1285, 1996) and Oliyai and Stella (Ann. Rev. Pharmacol. Toxicol., 32:521-544, 1993).

In addition, the properties of hydrophilicity and hydrophobicity of the compositions contemplated for use in the disclosure are well balanced, thereby enhancing their utility for both in vitro and especially in vivo uses, while other compositions lacking such balance are of substantially less utility. Specifically, compositions contemplated for use in the disclosure have an appropriate degree

of solubility in aqueous media which permits absorption and bioavailability in the body, while also having a degree of solubility in lipids which permits the compounds to traverse the cell membrane to a putative site of action. Thus, antibody compositions contemplated are maximally effective when they can be delivered to the site of target antigen activity.

In one aspect, methods of the disclosure include a step of administration of a CD37-specific binding molecule composition. In certain embodiments, the combinations of compounds may be administered concurrently, together in the same pharmaceutically acceptable carrier, or separately (but concurrently). In other embodiments, the CD37 immunotherapeutic (*i.e.*, the CD37-specific binding molecule) and a bifunctional chemotherapeutic can be administered sequentially, in any order and in any combination.

The binding molecule, bifunctional chemotherapeutic, or combination compositions may be administered orally, topically, transdermally, parenterally, by inhalation spray, vaginally, rectally, or by intracranial injection, or any combination thereof. In one embodiment, both the CD37-specific binding molecule and the bifunctional chemotherapeutic are administered parenterally, either concurrently or sequentially. 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.

In one embodiment, 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 disclosure implanted near the cancer.

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.

Binding molecule, bifunctional chemotherapeutic, or combination compositions of this disclosure may comprise one or more than one binding molecule, bifunctional chemotherapeutic, or any combination thereof. Also contemplated by the present disclosure is the administration of binding molecule, bifunctional chemotherapeutic, or combination compositions in conjunction with a further therapeutic agent. Further therapeutic contemplated by the disclosure are listed in paragraphs below.

A further therapeutic agent may be a B-cell-associated molecule. Other B-cell-associated molecules contemplated by the disclosure include binding molecules which bind to B-cell surface molecules that are not CD37. B-cell-associated molecules, include CD19 (B-lymphocyte antigen CD19, also referred to as B-lymphocyte surface antigen B4, or Leu-12), CD20, CD21, CD22 (B-cell receptor CD22, also referred to as Leu-14, B-lymphocyte cell adhesion molecule, or BL-CAM), CD23, CD40 (B-cell surface antigen CD40, also referred to as Tumor Necrosis Factor receptor superfamily member 5, CD40L receptor, or Bp50), CD80 (T lymphocyte activation antigen CD80, also referred to as Activation B7-1 antigen, B7, B7-1, or BB1), CD86 (T lymphocyte activation antigen CD86, also referred to as Activation B7-2 antigen, B70, FUN-1, or BU63), CD137 (also referred to as Tumor Necrosis Factor receptor superfamily member 9), CD152 (also referred to as cytotoxic T-lymphocyte protein 4 or CTLA-4), L6 (Tumor-associated antigen L6, also referred to as Transmembrane 4 superfamily member 1, Membrane component surface marker 1, or M3S1), CD30 (lymphocyte activation antigen CD30, also referred to as Tumor Necrosis Factor receptor superfamily member 8, CD30L receptor, or Ki-1), CD50 (also referred to as Intercellular adhesion molecule-3 (ICAM3), or ICAM-R), CD54 (also referred to

as Intercellular adhesion molecule-1 (ICAM1), or Major group rhinovirus receptor), B7-H1 (ligand for an immunoinhibitory receptor expressed by activated T cells, B-cells, and myeloid cells, also referred to as PD-L1; see Dong, et al., "B7-H1, a third member of the B7 family, co-stimulates T-cell proliferation and interleukin-10 secretion," Nat. Med., 5:1365-1369 (1999), CD134 (also referred to as Tumor Necrosis Factor receptor superfamily member 4, OX40, OX40L receptor, ACT35 antigen, or TAX-transcriptionally activated glycoprotein 1 receptor), 41BB (4-1BB ligand receptor, T-cell antigen 4-1BB, or T-cell antigen ILA), CD153 (also referred to as Tumor Necrosis Factor ligand superfamily member 8, CD30 ligand, or CD30-L), CD154 (also referred to as Tumor Necrosis Factor ligand superfamily member 5, TNF-related activation protein, TRAP, or T cell antigen Gp39), Toll receptors, or the like.

Examples of chemotherapeutic agents contemplated as further therapeutic agents include alkylating agents, such as nitrogen mustards (e.g., mechlorethamine, cyclophosphamide, ifosfamide, melphalan, and chlorambucil); nitrosoureas (e.g., carmustine (BCNU), lomustine (CCNU), and semustine (methyl-CCNU)); ethyleneimines and methyl-melamines (e.g., triethylenemelamine (TEM), triethylene thiophosphoramide (thiotepa), and hexamethylmelamine (HMM, altretamine)); alkyl sulfonates (e.g., buslfan); and triazines (e.g., dacabazine (DTIC)); antimetabolites, such as folic acid analogues (e.g., methotrexate, trimetrexate, and pemetrexed (multi-targeted antifolate)); pyrimidine analogues (such as 5-fluorouracil (5-FU), fluorodeoxyuridine, gemcitabine, cytosine arabinoside (AraC, cytarabine), 5-azacytidine, and 2,2'-difluorodeoxycytidine); and purine analogues (e.g, 6-mercaptopurine, 6-thioguanine, azathioprine, 2'-deoxycoformycin (pentostatin), erythrohydroxynonyladenine (EHNA), fludarabine phosphate, 2-chlorodeoxyadenosine (cladribine, 2-CdA)); Type I topoisomerase inhibitors such as camptothecin (CPT), topotecan, and irinotecan; natural products, such as epipodophylotoxins (e.g., etoposide and teniposide); and vinca alkaloids (e.g., vinblastine, vincristine, and vinorelbine); anti-tumor antibiotics such as actinomycin D, doxorubicin, and bleomycin; radiosensitizers such as 5-bromodeozyuridine, 5-iododeoxyuridine, and bromodeoxycytidine; platinum

coordination complexes such as cisplatin, carboplatin, and oxaliplatin; substituted ureas, such as hydroxyurea; and methylhydrazine derivatives such as N-methylhydrazine (MIH) and procarbazine.

Further therapeutic agents contemplated by this disclosure 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.

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 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 azathioprine, cyclophosphamide, cyclosporine, methotrexate, penicillamine, leflunomide, sulfasalazine, hydroxychloroquine, Gold (oral (auranofin) and intramuscular) and minocycline.

It is contemplated the binding molecule composition and the further therapeutic 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, for example, within minutes, hours or days of each other.

In another aspect, the further therapeutic agent is administered prior to administration of the binding molecule, bifunctional chemotherapeutic, or combination composition. Prior administration refers to administration of the further therapeutic agent within the range of minutes, hours, or one week prior to treatment with the binding molecule, bifunctional chemotherapeutic, or combination composition. It is further contemplated that the further therapeutic agent is administered subsequent to administration of the binding molecule composition. Subsequent administration is meant to describe administration more than minutes, hours, or weeks after binding molecule, bifunctional chemotherapeutic, or combination composition treatment or administration.

It is further contemplated that when the binding molecule is administered in combination with a further therapeutic agent, wherein the further therapeutic 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.

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.

The administration of the binding molecule, bifunctional chemotherapeutic or combination 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, for example, 70%, 80%, 90% of a subject's baseline value or normal range. Further, the administration of binding molecule, bifunctional chemotherapeutic, or combination composition of this disclosure results in desired clinical effects in the disease or disorder being treated.

In some embodiments, patients suffering from a disease associated with aberrant B cell activity who receive treatment according to the disclosure may demonstrate an overall beneficial response to the treatment, based on clinical criteria well known and commonly used in the art and as described below.

For example, in patients affected by rheumatoid arthritis, the administration may improve 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.

In a related aspect, the effects of combination administration on other diseases may be 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.

It is further contemplated that adult and juvenile myositis patients treated according to the disclosure may 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).

It is further contemplated that SLE patients treated according to the disclosure may 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).

It is further contemplated that multiple sclerosis patients treated according to the disclosure may 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).

It is further contemplated that patients suffering from IIM treated according to the disclosure may 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

may result 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.

In some embodiments, patients suffering from a B cell cancer that receive treatment according to the disclose may demonstrate an overall beneficial response to the treatment, based on clinical criteria well-known and commonly used in the art, and as described below, such as a decrease in tumor size, decrease in tumor number and/or an improvement in disease symptoms.

Exemplary clinical criteria are provided by the U.S. National Cancer Institute (NCI), which has divided some of the classes of cancers into the clinical categories of "indolent" and "aggressive" lymphomas. Indolent lymphomas include follicular cell lymphomas, separated into cytology "grades," diffuse small lymphocytic lymphoma/chronic lymphocytic leukemia (CLL), lymphoplasmacytoid/Waldenstrom's Macroglobulinemia, Marginal zone lymphoma and Hairy cell leukemia. Aggressive lymphomas include diffuse mixed and large cell lymphoma, Burkitt's lymphoma/diffuse small non-cleaved cell lymphoma, Lymphoblastic lymphoma, Mantle cell lymphoma and AIDS-related lymphoma. In some cases, the International Prognostic Index (IPI) is used in cases of aggressive and follicular lymphoma. Factors to consider in the IPI include age (<60 years of age versus >60 years of age), serum lactate dehydrogenase (levels normal versus elevated), performance status (0 or 1 versus 2-4) (see definition below), disease stage (I or II versus III or IV), and extranodal site involvement (0 or 1 versus 2-4). Patients with 2 or more risk factors have less than a 50% chance of relapse-free and overall survival at 5 years.

Performance status in the aggressive IPI is defined as follows: Grade Description: 0 Fully active, able to carry on all pre-disease performance without restriction; 1 Restricted in physically strenuous activity but ambulatory

and able to carry out work of a light or sedentary nature, e.g., light house work, office work; 2 Ambulatory and capable of all selfcare but unable to carry out any work activities, up to and about more than 50% of waking hours; 3 Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours; 4 Completely disabled, unable to carry on any selfcare, totally confined to bed or chair; and, 5 Dead. (See, The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. *N. Engl. J. Med.* 329:987–94, 1993.)

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.

The Ann Arbor classification system is also used to measure progression of tumors, especially non-Hodgkin's 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.

In one aspect, a therapeutic effect of the methods according to the disclosure 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 embodiment, the individual receiving treatment according to the invention demonstrates at least a partial response to treatment.

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.

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.

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.

In another 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.

As an additional aspect, the disclosure includes kits which comprise one or more compounds or compositions useful in the methods of this disclosure packaged in a manner which facilitates their use to practice methods of the disclosure. In a simplest embodiment, such a kit includes a compound or composition described herein as useful for practice of a method of the disclosure 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 of the disclosure. 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 of the disclosure.

EXAMPLES

EXAMPLE 1

CD37-SPECIFIC BINDING MOLECULES

Various CD37-specific binding proteins can be made with exemplary components provided in Tables 2-4. For example, antibodies or SMIP molecules can be made, and these molecules can be chimeric, humanized, or human. More specifically, preferred light chain variable region CDRs are found in SEQ ID NOS:236-240 and 247-254 and preferred heaving chain variable domain CDRs include SEQ ID NOS:241-245 and 247-254. Also, preferred light and heavy chain variable regions are provided in SEQ ID NOS:236-240 and SEQ ID NOS:241-245, respectively. Preferred light and heavy chain variable regions may also be found in SEQ ID NOS:247-254. Preferred variable domain linkers include SEQ ID NOS:225-229, while preferred hinges include SEQ ID NOS:230-235.

A particularly preferred embodiment is CAS-024 [G28-1 VH (M99F, Y102S) – VL (T25A) scFv (SSC-P) H WCH2 WCH3], which is a recombinant, 483 amino acid single-chain fusion protein that binds to human CD37. The binding domain comprises a humanized scFv based on the G28-1 antibody variable region CDRs, including mutations in the heavy chain CDR3 and in the light chain CDR1. The variable domains are linked by a $(G_4S)_5$ (25 amino acid) sequence (SEQ ID NO:229), which is connected via a three amino acid junction (GDQ) to the amino terminus of a modified upper and core IgG1 hinge region (wherein the first two of three cysteines found in these hinge regions are each substituted with a serine). The carboxy-terminus of the hinge is fused to an effector domain comprising CH2 and CH3 domains of IgG_1. The amino acid sequence of CAS-024 is set out in SEQ ID NO:253. Figure 1 shows heavy and light chain variable region amino acid sequence alignments of mouse G28.1 and CAS-024 sequences, along with a consensus identity sequence.

Table 1.

Exemplary CD-37 Specific SMIP Constructs

Construct	Description†	Linker	Hinge*	AA SEQ ID NO.
CAS-001	Vk3:VH5-51	16aa $(G_4S)_2(G_4T)G$	SSC-P	6
CAS-002	Vk3:VH5 JH4 *CDRL1 (T25A); CDRH3 (M99F)*	16aa $(G_4S)_2(G_4T)G$	SSC-P	48
CAS-003	Vk3:VH5 JH5a *CDRL1 (T25A); CDRH3 (M99F; Y102S)*	16aa $(G_4S)_2(G_4T)G$	SSC-P	52
CAS-007	Vk3:VH5-51 (*Linker TG→SS)*	16aa $(G_4S)_3S$	SSC-P	8
CAS-008	Vk3:VH5-51 *VH V11S*	16aa $(G_4S)_2(G_4T)G$	SSC-P	10
CAS-009	Vk3:VH5-51 *CDRL1 (E27Q)*	16aa $(G_4S)_2(G_4T)G$	SSC-P	12
CAS-010	Vk3:VH5-51 *CDRL1 (N28S)*	16aa $(G_4S)_2(G_4T)G$	SSC-P	14
CAS-011	Vk3:VH5-51 *CDRL1 (T25A)*	16aa $(G_4S)_2(G_4T)G$	SSC-P	16
CAS-012	mVk:VH5-5a	16aa $(G_4S)_2(G_4A)S$	SSC-P	18
CAS-013	Vk3:VH5 *VH3 FW1*	16aa $(G_4S)_2(G_4A)S$	SSC-P	22
CAS-014	mVH:Vk3	22aa $(G_4S)_4AS$	SSC-P	24
CAS-015	Vk3:mVH *(2H7 Leader)*	16aa $(G_4S)_2(G_4A)S$	SSC-P	26
CAS-016	mVH:Vk3	22aa $(G_4S)_4AS$	SCC-P	28
CAS-017	Vk3:mVH	16aa $(G_4S)_2(G_4A)S$	SSC-P	30
CAS-018	Vk3:mVH	16aa $(G_4S)_2(G_4A)S$	SCC-P	32
CAS-019	Vk3:VH5 *VH3 FW1*	16aa $(G_4S)_2(G_4A)S$	SCC-P	34
CAS-020	Vk3:VH5 *VH3-13 FW1*	16aa $(G_4S)_2(G_4A)S$	SSC-P	38
CAS-021	Vk3:VH5 *VH3-13 FW1*	16aa $(G_4S)_2(G_4A)S$	SCC-P	40
CAS-022	Vk3:VH5 *VH3-13 V11S FW1*	16aa $(G_4S)_2(G_4A)S$	SSC-P	42
CAS-023	Vk3:VH5 *VH3-13 V11S FW1*	16aa $(G_4S)_2(G_4A)S$	SCC-P	44
CAS-024	VHVL	25aa $(G_4S)_5$	SSC-P	253
CAS-060	Vk3:VH5 *VH3 FW1*	16aa $(G_4S)_2(G_4A)S$	SSC-P	36
CAS-061	Vk3:VH5 *CDRL1 (T25A, E27Q)*	16aa $(G_4S)_2(G_4T)G$	SSC-P	46
CAS-062	Vk3:CDR-H3 JH6 *CDRL1 (T25A);*	16aa	SSC-P	254

Construct	Description†	Linker	Hinge*	AA SEQ ID NO.
	CDRH3 (Y102V)	$(G_4S)_2(G_4T)G$		
CAS-063	Vk3:VH5 JH5b *CDRL1 (T25A); CDRH3 (M99F; Y102P)*	16aa $(G_4S)_2(G_4T)G$	SSC-P	266
CAS-064	Vk3:VH5 JH1 *CDRL1 (T25A) CDRH3 (D101E; Y102H)*	16aa $(G_4S)_2(G_4T)G$	SSC-P	267
CAS-065	Vk3:CDR-H3 JH3a *CDRL1 (T25A) CDRH3 (M99F; Y102V)*	16aa $(G_4S)_2(G_4T)G$	SSC-P	268
CAS-066	Vk3:CDR-H3 JH3b *CDRL1 (T25A) CDRH3 (M99F; Y102I)*	16aa $(G_4S)_2(G_4T)G$	SSC-P	269
CAS-067	Vk3:CDR-H3 JH2 *CDRL1 (T25A) CDRH3 (M99F; Y102L)*	16aa $(G_4S)_2(G_4T)G$	SSC-P	80
CAS-068	Vk3:VH5 JH2 *CDRL1 (T25A) CDRH2 (T59N; N61A; R62Q; K65Q)*	16aa $(G_4S)_2(G_4A)S$	SSC-P	82
CAS-069	Vk3:VH5 JH2 *CDRL1 (T25A) CDRH2 (T59G; N61A; R62Q; K65Q)*	16aa $(G_4S)_2(G_4A)S$	SSC-P	262
CAS-070	Vk3:VH5 JH5a *CDRL1 (T25A); CDRH3 (M99F; Y102S)*	20aa $(G_4S)_3(G_3A)S$	CPPCP	84

* Entries represent abbreviations regarding IgG1 hinges having mutations in only the first or the first and second cysteines found within the upper and core regions. The only exception is SEQ ID NO:84, which depicts the full-length hinge amino acid (CPPCP, SEQ ID NO:230)sequence used (essentially, only the core IgG1 seqeunce with a proline at the end).

† CDR mutation numbering is based on the Kabat numbering scheme.

Additional hinge regions that may be used in CD-37 specific binding molecules, such as SMIP molecules or antibodies, are provided in the following table.

Table 2.

Exemplary Hinge Regions for CD37-Specific Binding Proteins

Hinge description	Amino Acid Sequence	SEQ ID NO:
ccc(p)-hIgG1	EPKSCDKTHTCPPCP	90
scc(p)-hIgG1	EPKSSDKTHTCPPCP	92
scc(s)-hIgG1	EPKSSDKTHTCPPCS	94
csc(p)-hIgG1	EPKSCDKTHTSPPCP	102
csc(s)-hIgG1	EPKSCDKTHTSPPCS	104
ccs(p)-hIgG1	EPKSCDKTHTCPPSP	255
ccs(s)-hIgG1	EPKSCDKTHTCPPSS	256
ssc(p)-hIgG1	EPKSSDKTHTSPPCP	106
ssc(s)-hIgG1	EPKSSDKTHTSPPCS	108
scs(p)-hIgG1	EPKSSDKTHTCPPSP	257

Hinge description	Amino Acid Sequence	SEQ ID NO:
scs(s)-hIgG1	EPKSSDKTHTCPPSS	96
css(p)-hIgG1	EPKSCDKTHTSPPSP	110
css(s)-hIgG1	EPKSCDKTHTSPPSS	112
sss(p)-hIgG1	EPKSSDKTHTSPPSP	98
sss(s)-hIgG1	EPKSSDKTHTSPPSS	100
hIgA1	VPSTPPTPSPSTPPTPSPS	115
hIgA2	VPPPPP	116
hIgG3	ELKTPLGDTTHTCPRCPEPKSCDTPPPCPRCPEPKSCDTPPPCPRCPEPKSCDTPPPCPRCP	118
hIgG3(ccc)	EPKSCDTPPPCPRCP	258
hIgG3(scc)	EPKSSDTPPPCPRCP	120
hIgG3(csc)	EPKSCDTPPPSPRCP	126
hIgG3(ccs)	EPKSCDTPPPCPRSP	259
hIgG3(ssc)	EPKSCDTPPPSPRCP	260
hIgG3(scs)	EPKSCDTPPPCPRSP	261
hIgG3(css)	EPKSCDTPPPSPRSP	122
hIgG3(sss)	EPKSSDTPPPSPRSP	124
hIgD	ESPKAQASSVPTAQPQAEGSLAKATTAPATTRNTGRGGEEKKKEKEKEEQEERETKTP	127

Additional framework regions that may be used in CD-37 specific binding molecules, such as SMIP molecules or antibodies, are provided in the following tables.

TABLE 3A.

Human Heavy Chain Framework Regions for CD37-Specific Binding Proteins

V-region	Human VH Framework Regions	SEQ ID NO.
	FR1	
VH1	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	140
VH1	QVQLVQSGAEVKKPGSSVKVSCKASGGTFS	141
VH1	EVQLVQSGAEVKKPGATVKISCKVSGYTFT	143
VH5	EVQLVQSGAEVKKPGESLKISCKGSGYSFT	144
VH5	EVQLVQSGAEVKKPGESLRISCKGSGYSFT	145
VH7	QVQLVQSGSELKKPGASVKVSCKASGYTFT	146
	FR2	

V-region	Human VH Framework Regions	SEQ ID NO.
VH1	WVRQAPGQGLEWMG	147
VH1	WVQQAPGKGLEWMG	150
VH5	WVRQMPGKGLEWMG	151
	FR3	
VH1	RVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR	154
VH1	RVTITADESTSTAYMELSSLRSEDTAVYYCAR	155
VH1	RVTITADKSTSTAYMELSSLRSEDTAVYYCAR	156
VH1	RVTITADTSTDTAYMELSSLRSEDTAVYYCAT	157
VH5	QVTISADKSISTAYLQWSSLKASDTAMYYCAR	158
VH5	HVTISADKSISTAYLQWSSLKASDTAMYYCAR	159
VH7	RFVFSLDTSVSTAYLQISSLKAEDTAVYYCAR	160
	FR4	
JH1, JH4, JH5a, JH5b	WGQGTLVTVSS	161
JH2	WGRGTLVTVSS	162
JH3a, JH3b	WGQGTMVTVSS	163
JH6	WGQGTTVTVSS	168
	WGKGTTVTVSS	169

TABLE 3B.

Human Light Chain Framework Regions for CD37-Specific Binding Proteins

V-region	Human VK Framework Regions	SEQ ID NO.
	FR1	
VK3	EIVMTQSPATLSVSPGERATLSC	170
VK3	EIVLTQSPATLSLSPGERATLSC	171
VK1	DIQMTQSPSSLSASVGDRVTITC	172
VK1	NIQMTQSPSAMSASVGDRVTITC	175
VK1	AIQLTQSPSSLSASVGDRVTITC	177
VK1	DIQLTQSPSFLSASVGDRVTITC	178
VK1	AIRMTQSPFSLSASVGDRVTITC	179
VK1	AIQMTQSPSSLSASVGDRVTITC	180
VK1	DIQMTQSPSTLSASVGDRVTITC	181
	FR2	
VK3	WYQQKPGQAPRLLIY	182
VK1	WYQQKPGKAPKLLIY	184

V-region	Human VK Framework Regions	SEQ ID NO.
VK1	WYQQKPGKVPKLLIY	185
VK1	WYQQKPGKAPKRLIY	186
VK1	WFQQKPGKVPKHLIY	187
VK1	WFQQKPGKAPKSLIY	188
VK1	WYQQKPAKAPKLFIY	191
	FR3	
VK3	GIPARFSGSGSGTEFTLTISSLQSEDFAVYYC	194
VK3	GIPARFSGSGSGTDFTLTISSLEPEDFAVYYC	195
VK1	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	196
VK1	GVPSRFSGSGSGTDFTLTISSLQPEDVATYYC	197
VK1	GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC	198
VK1	GVPSRFSGSGSGTDYTLTISSLQPEDFATYYC	203
VK1	GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC	205
	FR4	
JK1	FGQGTKVEIK	206
	FGQGTKLEIK	207
	FGPGTKVDIK	208
	FGGGTKVEIK	209
	FGQGTRLEIK	210

Preferred exemplary component parts of CD-37 specific SMIP molecules (including leader sequences used for expression and export, but which are removed from the mature fusion protein when exported from a cell; linker sequences used to join light and heavy chain variable domains to form scFv binding domains; hinges used to join scFv binding domains to effector domains; and effector domains), as well as certain CD-37 specific SMIP molecules, including the preferred CAS-024 fusion protein, are provided in Table 4.

Table 4.

SMIP Component Parts and Select CD37-Specific SMIP Polypeptides

Construct No.	SEQ ID NO.	Amino Acid Sequence
Leader Sequence	223	MDFQVQIFSFLLISASVIIARGV
Leader Sequence	224	MEAPAQLLFLLLLWLPDTTG

Construct No.	SEQ ID NO.	Amino Acid Sequence
Variable Domain Linker	225	GGGGSGGGGSGGGGSS
Variable Domain Linker	226	GGGGSGGGGSGGGGAS
Variable Domain Linker	227	GGGGSGGSGSGGGGAS
Variable Domain Linker	228	GGGGSGGGGSGGGGTG
Variable Domain Linker	229	GGGGSGGGGSGGGGSGGGGSGGGGS
Hinge	230	CPPCP
Hinge (junction amino acid italicized)	231	*S*EPKSSDKTHTSPPCP
Hinge (junction amino acids italicized)	232	*DL*EPKSSDKTHTSPPCP
Hinge (junction amino acids italicized)	233	*DQ*EPKSSDKTHTSPPCP
Hinge (junction amino acids italicized)	234	*GDQ*EPKSSDKTHTSPPCP
Hinge (junction amino acids italicized)	235	*GSS*EPKSSDKTHTSPPCP
Mouse CD37 VL (CDRs highlighted)	236	DIQMTQSPASLSASVGETVTITC***RTSENVYSYLA***WYQQKQ GKSPQLLVS***FAKTLAE***GVPSRFSGSGSGTQFSLKISSLQPE DSGSYFC***QHHSDNPWT***FGGGTELEIK
Humanized CD37 VL (CDRs highlighted)a	237	EIVLTQSPATLSLSPGERATLSC***RTSENVYSYLA***WYQQKPG QAPRLLIY***FAKTLAE***GIPARFSGSGSGTDFTLTISSLEPEDF AVYYC***QHHSDNPWT***FGQGTKVEIK
Humanized CD37 VL (CDRs highlighted)b	238	EIVLTQSPATLSLSPGERATLSC***RASENVYSYLA***WYQQKPG QAPRLLIY***FAKTLAE***GIPARFSGSGSGTDFTLTISSLEPEDF AVYYC***QHHSDNPWT***FGQGTKVEIK
Humanized CD37 VL (CDRs highlighted)c	239	EIVLTQSPATLSLSPGERATLSC***RTSQNVYSYLA***WYQQKPG QAPRLLIY***FAKTLAE***GIPARFSGSGSGTDFTLTISSLEPEDF AVYYC***QHHSDNPWT***FGQGTKVEIK
Humanized CD37 VL (CDRs	240	EIVLTQSPATLSLSPGERATLSC***RTSESVYSYLA***WYQQKPG QAPRLLIY***FAKTLAE***GIPARFSGSGSGTDFTLTISSLEPEDF

Construct No.	SEQ ID NO.	Amino Acid Sequence
highlighted)d		AVYYC***QHHSDNPWT***FGQGTKVEIK
Mouse CD37 VH (CDRs highlighted)	241	AVQLQQSGPESEKPGASVKISCKASGYSFT***GYNMN***WVKQ NNGKSLEWIG***NIDPYYGGTTYNRKFKG***KATLTVDKSSSTA YMQLKSLTSEDSAVYYCAR***SVGPMDY***WGQGTSVTVSS
Humanized CD37 VH (CDRs highlighted)a	242	EVQLVQSGAEVKKPGESLKISCKGSGYSFT***GYNMN***WVRQ MPGKGLEWMG***NIDPYYGGTTYNRKFKG***QVTISADKSISTA YLQWSSLKASDTAMYYCAR***SVGPMDY***WGQGTLVTVSS
Humanized CD37 VH (CDRs highlighted)a	243	EVQLVQSGAEVKKPGESLKISCKGSGYSFT***GYNMN***WVRQ MPGKGLEWMG***NIDPYYGGTTYNRKFKG***QVTISADKSISTA YLQWSSLKASDTAMYYCAR***SVGPMDV***WGQGTLVTVSS
Humanized CD37 VH (CDRs highlighted)b	244	EVQLVQSGAEVKKPGESLKISCKGSGYSFT***GYNMN***WVRQ MPGKGLEWMG***NIDPYYGGTTYNRKFKG***QVTISADKSISTA YLQWSSLKASDTAMYYCAR***SVGPFDY***WGQGTLVTVSS
Humanized CD37 VH (CDRs highlighted)c	245	EVQLVQSGAEVKKPGESLKISCKGSGYSFT***GYNMN***WVRQ MPGKGLEWMG***NIDPYYGGTTYNRKFKG***QVTISADKSISTA YLQWSSLKASDTAMYYCAR***SVGPFDS***WGQGTLVTVSS
IgG1 CH2CH3	246	APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV YTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK
CAS-006 (chimeric anti-CD37 SMIP)	247	DIQMTQSPASLSASVGETVTITC***RTSENVYSYLA***WYQQKQ GKSPQLLVS***FAKTLAE***GVPSRFSGSGSGTQFSLKISSLQPE DSGSYFC***QHHSDNPWT***FGGGTELEIK*GGGGSGGGGSGGG GSS*AVQLQQSGPESEKPGASVKISCKASGYSFT***GYNMN***WV KQNNGKSLEWIG***NIDPYYGGTTYNRKFKG***KATLTVDKSSS TAYMQLKSLTSEDSAVYYCAR***SVGPMDY***WGQGTSVTVS S*DLEPKSSDKTHTSPPCP*APELLGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLT VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Construct No.	SEQ ID NO.	Amino Acid Sequence
CAS-001	248	EIVLTQSPATLSLSPGERATLSC***RTSENVYSYLA***WYQQKPG QAPRLLIY***FAKTLAE***GIPARFSGSGSGTDFTLTISSLEPEDF AVYYC***QHHSDNPWT***FGQGTKVEIK*GGGGSGGGGSGGGG TG*EVQLVQSGAEVKKPGESLKISCKGSGYSFT***GYNMN***WV RQMPGKGLEWMG***NIDPYYGGTTYNRKFKG***QVTISADKSI STAYLQWSSLKASDTAMYYCAR***SVGPMDY***WGRGTLVTV SS*DQEPKSSDKTHTSPPCP*APELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
CAS-002	249	EIVLTQSPATLSLSPGERATLSC***RASENVYSYLA***WYQQKPG QAPRLLIY***FAKTLAE***GIPARFSGSGSGTDFTLTISSLEPEDF AVYYC***QHHSDNPWT***FGQGTKVEIK*GGGGSGGGGSGGGG TG*EVQLVQSGAEVKKPGESLKISCKGSGYSFT***GYNMN***WV RQMPGKGLEWMG***NIDPYYGGTTYNRKFKG***QVTISADKSI STAYLQWSSLKASDTAMYYCAR***SVGPFDY***WGQGTLVTV SS*DQEPKSSDKTHTSPPCP*APELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
CAS-003	250	EIVLTQSPATLSLSPGERATLSC***RASENVYSYLA***WYQQKPG QAPRLLIY***FAKTLAE***GIPARFSGSGSGTDFTLTISSLEPEDF AVYYC***QHHSDNPWT***FGQGTKVEIK*GGGGSGGGGSGGGG TG*EVQLVQSGAEVKKPGESLKISCKGSGYSFT***GYNMN***WV RQMPGKGLEWMG***NIDPYYGGTTYNRKFKG***QVTISADKSI STAYLQWSSLKASDTAMYYCAR***SVGPFDS***WGQGTLVTV SS*DQEPKSSDKTHTSPPCP*APELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Construct No.	SEQ ID NO.	Amino Acid Sequence
CAS-014 (mouse-human hybrid)	251	AVQLQQSGPESEKPGASVKISCKASGYSFT***GYNMN***WVKQ NNGKSLEWIG***NIDPYYGGTTYNRKFKG***KATLTVDKSSSTA YMQLKSLTSEDSAVYYCAR***SVGPMDY***WGQGTSVTVSS*G GGGSGGGGSGGGGSGGGGSAS*EIVLTQSPATLSLSPGERAT LSC***RTSENVYSYLA***WYQQKPGQAPRLLIY***FAKTLAE***GIPA RFSGSGSGTDFTLTISSLEPEDFAVYYC***QHHSDNPWT***FGQ GTKVEIK*GSSEPKSSDKTHTSPPCP*APELLGGPSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PGK
CAS-017 (human-mouse hybrid)	252	EIVLTQSPATLSLSPGERATLSC***RTSENVYSYLA***WYQQKPG QAPRLLIY***FAKTLAE***GIPARFSGSGSGTDFTLTISSLEPEDF AVYYC***QHHSDNPWT***FGQGTKVEIK*GGGGSGGGGSGGGG AS*AVQLQQSGPESEKPGASVKISCKASGYSFT***GYNMN***WV KQNNGKSLEWIG***NIDPYYGGTTYNRKFKG***KATLTVDKSSS TAYMQLKSLTSEDSAVYYCAR***SVGPMDY***WGQGTSVTVS S*SEPKSSDKTHTSPPCP*APELLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
CAS-024	253	EVQLVQSGAEVKKPGESLKISCKGSGYSFT***GYNMN***WVRQ MPGKGLEWMG***NIDPYYGGTTYNRKFKG***QVTISADKSISTA YLQWSSLKASDTAMYYCAR***SVGPFDS***WGQGTLVTVSS*G GGGSGGGGSGGGGSGGGGSGGGGS*EIVLTQSPATLSLSPG ERATLSC***RASENVYSYLA***WYQQKPGQAPRLLIY***FAKTLAE*** GIPARFSGSGSGTDFTLTISSLEPEDFAVYYC***QHHSDNPWT*** FGQGTKVEIK*GDQEPKSSDKTHTSPPCP*APELLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK

EXAMPLE 2

EXPRESSION OF CAS-024 AND OTHER CD37-SPECIFIC BINDING PROTEINS

CAS-024 and other CD37-specific binding SMIP molecules were cloned into a Chinese Hamster Ovary (CHO) mammalian cell expression system. Transfected CHO cells that produced the SMIP molecules were cultured in shake flasks and harvested cell culture supernatants were titered using Octec Q Protein A sensor.

Table 5 shows that the CAS-024 construct (VHVL format with 25 amino acid variable domain linker) had an unexpectedly superior expression level, up to about 10-fold better, than the other humanized anti-CD37 SMIP molecules (mostly VLVH format with 15 amino acid variable domain linker). Indeed, all fully humanized VLVH constructs expressed poorly (data not shown), as did mouse-human hybrid molecules in either orientation (*see* Example 5).

Table 5.

SMIP Expression

SMIP Protein	Clones Screened	Protein Titer Range (µg/ml)
CAS-001	492	65 – 80
CAS-002	425	200 – 280
CAS-003	611	300 – 360
CAS-024	203	500 – 650

EXAMPLE 3

PURIFICATION AND SIZE EXCLUSION CHROMATOGRAPHY OF CAS-024 AND OTHERCD37-SPECIFIC BINDING PROTEINS

To produce more protein, nucleic acid encoding CAS-024 and several other CD37-specific binding SMIP molecules were cloned into a Chinese Hamster Ovary (CHO) mammalian cell expression system. Transfected CHO cells that produced the SMIP molecules were cultured in shake flasks.

All of the CD37-specific binding SMIP molecules were purified from CHO culture supernatants by Protein A affinity chromatography. A 50 mL rProtein A FF Sepharose™ column (GE Healthcare) was equilibrated at 5.0 mls/min (150 cm/hr) for 1.5 column volumes (CV) with dPBS. The culture supernatant was loaded onto the rProtein A Sepharose™ FF column at a flow rate of 1.7mls/min using the AKTA Explorer 100 Air (GE healthcare), capturing the recombinant SMIP molecules. The column was washed with dPBS for 5 Column Volumes (CV), then 1.0 M NaCl, 20mM Sodium Phosphate, pH 6.0, and then with 25 mM NaCl, 25mM NaOAc, pH 5.0. The recombinant CD37-specific binding molecules were eluted from the column with 100mM glycine, pH 3.5. Fractions (10mL) of the eluted product were recovered and then brought to pH 5.0 with 20% of the eluted volume of 0.5 M 2-(N-morpholino)ethanesulfonic acid (MES), pH6.0. This eluted product was concentrated to approximately 25 mg/mL protein and filter sterilized.

This concentrated and sterilized protein was further purified by GPC size exclusion chromatography (SEC) to achieve separate SMIP (dimer) molecule from higher molecular weight aggregates. An XK 50/100 column (GE healthcare) containing 1 L of Superdex 200 FF Sepharose™ was equilibrated at 12.6 ml/min (38cm/hr) for 1.5 column volumes (CV) with dPBS. A maximum volume of 54 mls (3% CV) of sample was applied to the column. The column continued to run at 12.6 ml/min and the eluted protein was fractionated in 40 mL fractions. Each fraction was analyzed for product quality using an analytic HPLC, and the eluted fractions were pooled to greater than about 95% protein of interest (non-aggregated). The resultant pool was filter sterilized at 0.22 µm, concentrated, and then formulated with 20 mM sodium phosphate, 240 mM sucrose, pH 6.0.

The SEC traces showing the peaks containing the protein of interest (POI) for CAS-001 (SEQ ID NO:6), CAS-002 (SEQ ID NO:48), CAS-003 (SEQ ID NO:52), and CAS-024 (SEQ ID NO:253) are shown in Figures 2A-2D, respectively. The CAS-024 peak is narrower and more symmetric than the CAS-001, CAS-002, and CAS-003 samples (broader and asymmetric). The CAS-006 (chimeric) molecule produces a sharp peak similar to CAS-024. The CAS-001,

CAS-002, and CAS-003 samples all had a slight tailing shoulder, which if integrated, accounts for about 35% of the POI area. This 'shoulder' would be difficult to separate from the POI and probably represents either misfolded conformers or a heterogenous population of molecules (*e.g.*, have different levels of glycosylation). This indicates that CAS-024 was not only expressed better, but this construct also produces a more homogenous population of molecules.

EXAMPLE 4

CELL BINDING BY CAS-024 IS UNEXPECTEDLY SUPERIOR TO OTHER CD37-SPECIFIC BINDING PROTEINS

A competition assay was used to compare the binding affinity of different anti-CD37 specific small modular immunopharmaceutical (SMIP) molecules to CD-37 found on Ramos cells (a B-lymphoblastoid cell line derived from a Burkitt lymphoma). An SEC purified chimeric anti-CD37 SMIP molecule (CAS-006, SEQ ID NO:247) was labeled with the FMAT Blue® fluorescence dye (Applied Biosystems) and used as the standard to compete with purified unlabeled chimeric anti-CD37 SMIP molecule (positive control) and purified unlabeled humanized anti-CD37 SMIP test molecules. Higher affinity showed up as a weaker fluorescence signal and an FL1 fluorescence value was used to generate the competition curve. Briefly, the reagent FMAT Blue® labeled chimeric anti-CD37 SMIP molecule was diluted to 2µg/ml in FACS blocking buffer and the purified protein samples (CAS-001 (SEQ ID NO:6), CAS-002 (SEQ ID NO:48), CAS-003 (SEQ ID NO:52), and CAS-024 (SEQ ID NO:253)) were serially diluted 1:2 to concentrations ranging from 50 µg/ml to 0.02 µg/ml. Ramos cells were harvested at 1,000 rpm for 5 minutes and resuspend in FACS blocking buffer at 4 x 10^6 cells/10 ml buffer. To each well of a black 96-well plate the following was added: 50 µl sample, 50 µl FMAT Blue® labeled chimeric anti-CD37 SMIP molecule, and 50 µl Ramos cells (4 x 10^4 /well). The plates were incubated at room temperature for 30 min and read on an 8200 Cellular Detection System (Applied Biosystems) gated for middle cell size and low signal.

This FMAT competition assay showed that CAS-024 (humanized anti-CD37 SMIP molecule having a VHVL scFv with a 25 amino acid variable domain linker) has the same affinity for CD37 as the parent chimeric anti-CD37 SMIP molecule and, in contrast, has an unexpectedly up to a 4-fold greater affinity for CD37 than the humanized anti-CD37 SMIP molecules having the reverse VLVH structure and a shorter 16 amino acid variable domain linker (*see* Figure 3). The best binding, although still significantly less than CAS-006 or CAS-024, was found in a VLVH construct that does not have any CDR mutations (CAS-001). However, CAS-001 was consistently the worst expressing construct and produced a non-homogenous population of purified molecules – even for this construct, CAS-024 bound from 1.5- to 2-fold better than CAS-001.

This result was also surprising because M99 and Y102 in the heavy chain CDR3 of CAS-024 are mutated – the Y102 position is generally conserved and it would be expected that a change at this position alone would diminish or even abolish binding (*e.g.*, CAS-062, mutated at postion Y102, has detectable but severely decreased binding compared to CAS-001 or CAS-024, while CAS-063 to CAS-067 each have barely detectable to no binding activity in this assay when a mutation at postion M99 or D101 is added, data not shown). Thus, the structure of CAS-024 provided a molecule that surprisingly bound as well as the chimeric molecule, CAS-006.

EXAMPLE 5

EXPRESSION AND CELL BINDING OF CAS-024 COMPARED TO MOUSE-HUMAN HYBRID CD37-SPECIFIC BINDING PROTEINS

CAS-024 and other CD37-specific binding SMIP molecules were produced by recombinant DNA technology and transfected into HEK293 cells for 7 days. Cell culture supernatants were harvested on day 7 and titered using Octec Q Protein A sensor.

Similar to the results found in Example 2, here Table 6 shows that CAS-024 (VHVL format with 25 amino acid variable domain linker) expressed from about 5-fold to about 27-fold better than the other humanized or mouse-

human hybrid anti-CD37 SMIP molecules. The mouse-human hybrid molecules did not express well regardless of the VHVL or VLVH orientation.

Table 6.

SMIP Expression

SMIP Protein	Protein Titer (µg/ml)
CAS-002 (hVLhVH)	0.47
CAS-003 (hVLhVH)	2.39
CAS-014 (mVHhVL)	2.16
CAS-017 (hVLmVH)	0.70
CAS-006 (mVLmVH)	9.3
CAS-024 (hVHhVL)	12.7

A competition assay as described in Example 4 was used to compare the binding affinity of different mouse-human hybrid anti-CD37 SMIP molecules compared to CAS-024 binding to Ramos cells. An SEC purified chimeric anti-CD37 SMIP molecule (CAS-006, SEQ ID NO:247) was labeled with the FMAT Blue® fluorescence dye (Applied Biosystems) and used as the standard to compete with purified unlabeled chimeric anti-CD37 SMIP molecule (CAS-006, positive control) and purified unlabeled humanized anti-CD37 SMIP test molecules – CAS-002 (SEQ ID NO:48), CAS-003 (SEQ ID NO:52), CAS-014 (SEQ ID NO:251), CAS-017 (SEQ ID NO:252), and CAS-024 (SEQ ID NO:253).

This FMAT competition assay again showed that CAS-024 (VHVL humanized molecule with a 25 amino acid linker) has the same affinity for CD37 as the parent chimeric anti-CD37 SMIP molecule (CAS-006), whereas CAS-002 and CAS-003 (VLVH humanized molecules with a 16 amino acid linker) did not bind as well (showing a 2- to 3-fold reduction) (*see* Figure 4A). The mouse-human hybrid molecules, regardless of variable domain orientation (mouseVH-humanizedVL with a 22 amino acid linker or humanizedVL-mouseVH with a 16 amino acid linker), bound as well as or even better than (1.5- to 2-fold) CAS-006 and CAS-024 (*see* Figure 4B). These data show that a mouse-human hybrid molecule without mutations binds as well as or better than CAS-006, regardless of orientation, and that a fully humanized VLVH construct with no CDR

mutations binds better than other humanized molecules but still has diminished binding compared to CAS-006 or CAS-024. Together, these data suggest that no mutations in CDRs for this molecule would be better binders. Also, the particular order (VLVH or VHVL) did not seem to solve the expression problem, even when a longer variable domain linker is used (see CAS-014). Thus, it was unpredictable to select a molecule with the CAS-024 structure and properties similar to the parent molecule CAS-006.

EXAMPLE 6

CAS-006 AND VARIOUS CD37-SPECIFIC ANTIBODIES BIND SAME OR AN OVERLAPPING EPITOPE ON CD37

Experiments were performed to identify the CD37 epitope bound by CAS-006 and other previously described CD37-specific antibodies. Unconjugated MB371 (#555457) and FITC-conjugated MB371 (#555456) were obtained from BD Pharmingen (San Jose, CA), FITC-conjugated BL14 (#0457) from Immunotech/Beckman Coulter (Fullerton, CA), FITC-conjugated NMN46 (#RDI-CBL 136FT) and unconjugated NMN46 (#RDI-CBL 136) from RDI (Flanders, NJ), FITC-conjugated IPO24 (#186-040) and unconjugated IPO-24 (#186-020) from Ancell Corporation (Bayport, MN), FITC-conjugated HHI (#3081) and unconjugated HH1 (#3080) from DiaTec.Com (Oslo, Norway) and FITC-conjugated WR17 (YSRTMCA483F) and unconjugated WR17 (YSRTMCA483S) from Accurate Chemical & Scientific (Westbury, NY). CAS-006 SMIP protein was produced as described in Example 2.

CAS-006 was conjugated to FITC using a Molecular Probes Fluororeporter FITC Labeling Kit (F6434) according to manufacturer's instructions as follows: CAS-006 protein peak of interest (POI) at 13.5 mg/mL was adjusted to 5 mg/mL with PBS. One mg (200 ul) was added to kit tubes with a stirbar, and 1M $NaHCO_3$ (adjusted to pH 8.5 with 6N NaOH), was added to a final concentration of 0.1M. 50 ul DMSO was added to 370 ug of FITC and was added to the tubes at molar ratios of 15, 20, 30 and 40 FITC: protein using the following formula to determine the ul of FITC to add: [µl of FITC solution to add =

5 mg/mL protein x 0.2 mL x 389 x 100 x desired molar ratio/Molecular weight of CAS-006 (110,000)].

Reactions were shielded from light and stirred continuously for 75 minutes at room temperature. Reactions were added to spin columns prepared as described in the kit and spun at 1100 g for 5 minutes to buffer exchange into PBS with azide and remove unconjugated FITC. The OD at 280 nM and 494 nM was determined with 2 ul drops on the Nanodrop; the extinction coefficient for CAS-016 was experimentally determined for this instrument by reading dilutions of the starting unconjugated SMIP molecule, the concentration of each of the conjugates was 4.25 mg/ml and the following FITC:protein rations were determined: 2.7 FITC/CAS-016 at a ratio of 15; 3.7 FITC/CAS-016 at a ratio of 20; 4.4 FITC/CAS-016 at a ratio of 30; and 5.1 FITC/CAS-016 at a ratio of 40.

BSA was added to 3 mg/mL to help stabilize the protein. Binding of each fraction was assessed at dilutions ranging from 100-24,300x on Ramos and 3200-25,600 on human PBMC. All bound, but the MR30 ratio was chosen for further use since it gave a high MFI that was well maintained over the titration range used, indicating that binding avidity was least affected in this reaction.

FITC labeled antibody conjugates were titrated from 10 ng/mL to 10 µg/mL in an initial binding study to determine the optimal amount to use in the blocking studies. The level chosen was just below saturating amounts, and was kept constant in the subsequent assays, while levels of blocking antibody were increased over a 10-fold range. Data were plotted as percent of maximal binding versus concentration of blocking antibody, so that higher levels indicate less efficient blocking, while lower levels indicate more efficient blocking activity. All of the antibodies tested showed blocking activity of the maximal binding observed without unlabeled reagents (Figure 5).

BJAB-cells, a lymphoblastoid B-cell line were then stained with a panel of various clones of anti-CD37 mAbs, including MB371, BL14, NMN46, IPO24, HH1, WR17, and chimeric CAS-006 SMIP.

For competitive binding assays, 2.5×10^5 BJAB cells were incubated in 96-well V-bottom plates in staining media (PBS with 2% mouse sera) with the FITC-conjugated anti-CD37 mAbs at 1.25 µg/mL in the presence of

unconjugated anti-CD37 MAb at the indicated concentrations (2.5, 1.25, 0.6, or 0.3 µg/ml) or staining media for 45 minutes on ice in the dark. Blocking antibodies and FITC labeled antibody conjugates were added to reactions prior to addition of cells. The cells were then washed 2.5 times with PBS and fixed with 1% paraformaldehyde (USB, Cleveland, Ohio). The treated cells were analyzed by flow cytometry using a FACsCalibur instrument and CellQuest software (BD Biosciences, San Jose, CA).

For FACs cross blocking assays, 2.5 x 10^5 BJAB cells were incubated in 96-well V-bottom plates in staining media (PBS with 2% mouse sera) in the presence of unconjugated anti-CD37 MAb at 5 µg/mL staining media for 45 minutes at room temperature in the dark. FITC-conjugated anti-CD37 mAbs were added to a final concentration of 2 µg/ml, resulting in a dilution of the unlabelled reagents to 3.3 µg/ml. The reactions were further incubated for 45 minutes at room temperature in the dark, then washed 2.5 times with PBS, and finally fixed in 1% paraformaldehyde in PBS (USB, Cleveland, Ohio). Cells were analyzed by flow cytometry on a FACsCalibur instrument using Cell Quest software (BD Biosciences, San Jose, CA).

For cell binding assays, cells were suspended in PBS (Gibco/Invitrogen, Grand Island NY) containing 2% FBS (Gibco/Invitrogen), (staining media) at a concentration of approximately 4 x 10^6 cells/mL. Cells were then plated and test samples, diluted in staining media, were then added 1:1 to the final designated concentrations. Reactions were incubated for 45 minutes on ice. Samples were centrifuged and washed 2 times with PBS. FITC goat anti-human IgG (CalTag, Burlingame CA) was added at a final dilution of 1:50, and incubated 45 minutes on ice. Samples were centrifuged, washed in PBS, then fixed in 200 µl 1% paraformaldehyde in PBS (USB, Cleveland, Ohio). Cells were analyzed by flow cytometry on a FACsCalibur instrument using Cell Quest software (BD Biosciences, San Jose, CA).

Each antibody showed dose dependent inhibition of binding, indicating that all the molecules tested bind to an identical or closely related epitope. A different potency for inhibition of binding was observed for each antibody. CAS-006 SMIP had the highest level of blocking activity of all

molecules tested, while HH1 gave an intermediate level of blocking activity, and WR17, IPO24 blocked better than MB371, but showed less effective blocking than the other two unlabeled molecules (Figure 5).

In addition to analysis of blocking activity, a similar series of experiments was performed in which various CD37 targeted antibodies were tested for their ability to compete with one another for binding to the CD37 receptor. The results from these experiments, like results obtained in the blocking studies for all the molecules tested, indicated that the various CD37 targeted antibodies and CAS-006 have the same or closely overlapping epitopes.

EXAMPLE 7

DOSE RESPONSE OF CAS-024 IN AN ESTABLISHED SUBCUTANEOUS HUMAN TUMOR (DOHH2) XENOGRAFT MODEL IN SCID MICE

The objective of this experiment was to examine the dose response to treatment with CAS-024 in a model of established subcutaneous human tumor (DOHH2) xenograft model in SCID mice. DOHH2 is a $CD20^{+}CD37^{+}$ human B-lymphoblastoid cell line derived from a patient with follicular lymphoma (Kluin-Nelemans *et al*., Leukemia 5:221, 1991). Thus, DOHH2 was derived from a patient with a non-Burkitt's NHL.

Five million DOHH2 cells were injected subcutaneously into the flank of female CB-17SCID mice (Harlan, Somerville, NJ) at 6.5 weeks of age and at a mean weight of 18.0 ± 0.1 g (ranging from 14.6 to 22.6 g). On day 8 post-tumor inoculation, palpable tumors were apparent in a majority of mice. The tumor-bearing mice were sorted into four groups with equivalent mean tumor volumes (n=14 per group; 2 cages of 5 mice and 1 cage of 4 mice for each group). The day of the sort was defined as day 0. Tumor diameters were determined with a pair of calipers and tumor volumes were calculated using the formula: $V=½\ [length \times (width)^2]$. The baseline mean tumor volume was 228 mm^3, the median baseline tumor size was 224 mm^3, and the range was 179 to 284 mm^3.

Table 7.

Reagents for In Vivo Use

Reagent	% POI	Concentration and Endotoxin	Preparation for Injection
PBS	NA	1X Endotoxin <0.03 EU/mg	NA
Human IgG (huIgG)	Not tested	10 mg/mL Endotoxin = 10 EU/mg	Diluted to 1.0 mg/mL PBS
CAS-024	100	9.6 mg/mL Endotoxin = 0.01 EU/mg	Diluted to 1.0 mg/mL PBS for 200 μg dose; then diluted 1:2 to prepare 100 μg dose, then serially diluted 1:3 to prepare the other dose solutions.

Tumor-bearing groups of SCID mice were treated on days 0, 4, and 8 via IP injection of 0.2 mL of PBS containing 200 μg of huIgG (negative control) or 200, 100, 30, 10, or 3 μg of CAS-024. The two lowest dose solutions of CAS-024 were prepared on the day of injection to avoid the need to add a carrier protein to the most dilute solutions. Drug solutions were color-coded as described below (see Table 8 below).

Table 8.

Experimental Design

Group ID	No. Mice, Route of Injection, and Treatment Days	Dose per injection (μg)	mg/kg per Injection[a]	Cumulative Dose (μg)	Cumulative Dose (~mg/kg)[a]
huIgG	14 per group IP injection Days 0, 4, 8	200	11.1	600	33
CAS-024 200		200	11.1	600	33
CAS-024 100		100	5.6	300	16.7
CAS-024 30		30	1.7	90	5.0
CAS-024 10		10	0.6	30	1.7
CAS-024 3		3	0.2	9	0.5

[a]Note that huIgG and CAS-024 were delivered in μg per mouse, not in mg/kg. The approximate mg/kg is noted for convenience, and is based on the mean weight (18.0 ± 0.1 g) of mice on day 0. The weight range in this experiment was 14.6 to 22.6 g.

Dose solutions were prepared in similar volumes and the contents of the tubes were noted on removable labels. An investigator who was not treating or assessing the mice placed a color code on each tube and noted the code and identity of the tube contents in a laboratory notebook. Mice were monitored daily by visual inspection. Weights were determined weekly, and tumor diameters were determined at least 3 times per week (M, W, F) by an observer blinded (see above) to the treatment groups. Tumor volumes were calculated as described above. Mice were euthanized if their tumor volume reached more than 1500 mm^3 (or 1200 mm^3 on Fridays). Death was not an endpoint in the tumor protocols and, unless noted otherwise, "survival" of a mouse was determined by the time it was euthanized due to its tumor volume reaching the predetermined limits. (The protocol called for mice to be euthanized if (1) their tumor volume exceeded the parameters noted above, (2) ulceration of a tumor occurred, (3) the tumor inhibited the mobility of the mouse, and (4) weight loss exceeded 20% of body weight.)

One mouse in the CAS-024 100 μg treatment group was euthanized on day 35 due to weight loss >20%. This mouse had a tumor volume of 266 mm^3 at that time, and was treated as censored data for the survival analysis (not euthanized as of day 35 due to tumor growth). For the calculation of tumor-free incidence at the end of the study, this mouse was classified as one that was euthanized during the study due to growth of its tumor (its tumor was growing back at the time of its death). No other mice were found dead and none were euthanized due to weight loss, tumor ulceration, or impaired mobility. No overt signs of toxicity or weight loss were observed in any of the treatment groups (data not shown).

All statistical analyses were performed using GraphPad Prism software. Significant differences in mean tumor volumes and mean relative tumor volumes were determined using a one-way ANOVA for nonparametric data (Kruskal-Wallis test) with Dunn's multiple comparison post test. To examine differences between each of the CAS-024 treated groups and the huIgG group, all groups were compared. For comparisons between the CAS-024 groups only, the huIgG group was excluded. In addition, the high and middle dose (200, 100,

and 30 µg) groups were analyzed as a one data set, and the middle and low dose (30, 10, and 3 µg) groups were analyzed as another data set. Significant differences in survival of mice over time were determined using Kaplan-Meier survival analysis with a log-rank test for comparing survival curves. Significant differences in the incidence of tumor-free mice were determined using Fisher's exact test. p values <0.05 were considered significant.

CAS-024 had a dose-dependent inhibitory effect on the growth of DOHH2 tumors. With the exception of the low (3 µg) dose regimen group, the mean tumor volume of each CAS-024 treated group was significantly lower than that of the human IgG treated group as early as day 5, and remained lower through day 12. The huIgG treated mice were euthanized starting on day 12; therefore, comparisons of tumor volumes of the CAS-024 treated groups to the huIgG group were not performed for later time points. In terms of a dose response, there was no significant difference in the mean tumor volumes of the two highest dose groups at any point in the study. In contrast, the mean tumor volumes of these two groups differed significantly from those of each of the three lower dose groups from days 12 through 16 (day 16 was the last evaluable timepoint for the low dose group). Similarly, the mean tumor volumes in mice of the 30 µg and 10 µg dose groups differed from each other and from the low dose group over this same period.

The tumors in the mice treated with huIgG grew rapidly, and all of the mice in this group were euthanized by day 19. As summarized in Tables 9 and 10 below, the survival of mice treated with any of the CAS-024 dose regimens was prolonged relative to the huIgG treated group ($p<0.0001$ in all cases). In terms of a dose response, there was no significant difference in the survival curves of mice treated with the highest (200 and 100 µg) dose regimens ($p=0.7091$). With the exception of this group comparison, there was a significant difference between the survival curve of each dose group and the survival curve of each of the groups treated with a lower dose regimen (p values ranged from 0.0132 to <0.0001).

Table 9.

Median Survival Time and Incidence of Tumor-Free Mice

Treatment Group[a]	Cumulative Dose	Median Survival Time (Days)[b]	Death (Not Due to Large Tumor Volume)	Tumor-Free Incidence at End of Study[c]	p Value for Fischer's Exact Test (comparison of tumor-free incidence)[d]
HuIgG 200	600 μg	14	0/14	0/14 (0%)	NA
CAS-024 200	600 μg	**Undefined[ef]**	0/14	**11/14 (79%)[g]**	<0.0001
CAS-024 100	300 μg	**Undefined**	**1/14[h]**	**11/14 (79%)**	<0.0001
CAS-024 30	90 μg	**35**	0/14	**5/14 (36%)**	0.0407
CAS-024 10	30 μg	**28**	0/14	0/14 (0%)	NA
CAS-024 3	9 μg	**19**	0/14	0/14 (0%)	NA

[a] Mice were treated with the indicated protein via IP injection on days 0, 4, and 8. The numbers indicate the amount of protein (μg) injected per day.

[b] "Survival" of a mouse was determined by the day it was euthanized due to tumor growth. One mouse in the CAS-024 100 μg dose group was euthanized on day 35 due to >20% weight loss. The mouse had a tumor volume of 266 mm^3 at that time, and was treated as censored data (tumor volume did not reach predetermined limit by day 35) for the Kaplan Meier analysis. No other mice were euthanized for reasons other than its tumor volume reaching the predetermined limit.

[c] "Tumor-free" mice had no palpable SC tumors. The absence of tumor cells was not confirmed by histology. The study ended on day 61.

[d] Each group was compared with the HuIgG treated control group.

[e] The median survival time is undefined when >50% of the mice are alive at the end of the observation period.

[f] Values in bold face indicate that the survival curves of the indicated group are significantly different from those of HuIgG control ($p<0.0001$ in each case, log rank test).

[g] Values in bold face are significantly different from the huIgG treated control group.

[h] One mouse was euthanized on day 35 due to >20% weight loss. The mouse had a tumor volume of 266 mm^3 at that time and was treated as censored data for the Kaplan Meier analysis.

Table 10.

p-Values for Comparison of Survival Curves and Tumor-Free Incidence Between CAS-024 Treated Groups

Group Comparison[a]	p Values for Indicated Comparisons	
	Log rank test (comparison of survival curves)	Fisher's exact test (comparison of tumor-free incidence)
200 vs 100	0.7091	1.0000
200 vs 30	**0.0132**[b]	0.0542
200 vs 10	**<0.0001**	**<0.0001**
200 vs 3	**<0.0001**	**<0.0001**
100 vs 30	**0.0035**	0.0542
100 vs 10	**<0.0001**	**<0.0001**
100 vs 3	**<0.0001**	**<0.0001**
30 vs 10	**0.0002**	**0.0407**
30 vs 3	**<0.0001**	**0.0407**
10 vs 3	**<0.0001**	NA

[a]See legend to Table 7 for information on the groups.

[b]p values <0.05 are in bold face for emphasis.

All of the mice in the huIgG treated group and in the two lowest (10 and 3 μg) CAS-024 dose groups were euthanized due to growth of their tumors. In contrast, the majority of tumors in the groups of mice treated with 200 or 100 μg of CAS-024 regressed to the point that no palpable tumor was present. By the end of the study, 11/14 (79%) of the mice in each of the two highest dose groups and 5/14 (36%) of the mice in the 30 μg dose group remained tumor-free ($p<0.0001$ and 0.0407, respectively, vs. huIgG group).

Thus, CAS-024 exhibited dose-dependent inhibitory effects on the growth of established subcutaneous human tumor (DOHH2) xenografts in SCID mice. The two highest dose regimens (100 or 200 μg per IP injection; cumulative dose of 300 or 600 μg, which corresponds to about 16.7 or 33 mg/kg, respectively) had similar inhibitory effects and were the most efficacious of the regimens tested in terms of inhibiting tumor growth, prolonging survival, and inducing complete tumor regression.

EXAMPLE 8

EFFICACY OF CAS-024 AND RITUXAN® AS SINGLE AGENTS IN AN ESTABLISHED HUMAN TUMOR (DOHH2) XENOGRAFT MODEL IN SCID MICE

The objective of this study was to examine the efficacy of CAS-024 and Rituxan as single agents in a model of established human tumor (DOHH2) xenografts in SCID mice. As set out above, DOHH2 is a $CD20^{+}CD37^{+}$ human B-lymphoblastoid cell line derived from a patient with follicular lymphoma.

Five million DOHH2 cells were injected subcutaneously into the flank of female CB-17SCID mice (Harlan, Somerville, NJ) at 6.5 weeks of age. On day 8 post-tumor inoculation, palpable tumors were apparent in a majority of the mice. The tumor-bearing mice were sorted into four groups (n=15 per group; 3 cages of 5 mice for each group) with equivalent mean tumor volumes. The day of the sort was defined as day 0 of the study. Tumor diameters were determined with a pair of calipers and tumor volumes were calculated using the formula: V=½ [length x $(width)^2]_3$. The baseline mean tumor volume was 228 mm^3; the median baseline tumor size was 227 mm; and the range was 181 to 272 mm^3. Mice (15 per treatment group) were treated on days 0, 4, and 8 via IP injection of 0.2 mL of PBS containing 200 µg human IgG, CAS-024, or Rituxan® (for a total of 600 µg after the three treatments). For the huIgG, CAS-024, and Rituxan® IP treated groups, solutions were prepared in similar volumes and the contents of the tubes were noted on removable labels. An investigator who was not treating or assessing the mice placed a color code on each tube and noted the code and identity of the tube contents in a laboratory notebook.

Mice were monitored daily by visual inspection. Weights were determined weekly, and tumor diameters were determined at least 3 times per week (M, W, F) by an observer blinded (see above) to the treatment groups. Tumor volumes were calculated as described above. Tumor volumes on the last day that all mice were alive in each group were also expressed in terms of tumor volumes relative to day 0, using the formula:

$$\text{Relative tumor volume on day of interest} = \frac{\text{(volume on day of interest – volume on day 0)}}{}$$

volume on day 0

Mice were euthanized if their tumor volume reached more than 1500 mm3 (or 1200 mm3 on Fridays). Death is not an endpoint in our tumor protocols, and unless noted otherwise, “survival” of a mouse was determined by the time it was euthanized due to its tumor volume reaching the predetermined limits. (Our protocol calls for mice to be euthanized if their tumor volume exceeds the parameters noted above, ulceration of a tumor occurs, the tumor inhibits the mobility of the mouse, or if weight loss exceeds 20%.)

All statistical analyses were performed using GraphPad Prism software. Significant differences in mean tumor volumes and mean relative tumor volumes were determined using a one-way ANOVA for nonparametric data (Kruskal-Wallis test) with Dunn’s multiple comparison post test. Significant differences in survival of mice over time were determined using Kaplan-Meier survival analysis with a log-rank test for comparing survival curves. Significant differences in the incidence of tumor-free mice were determined using Fisher’s exact test (p values <0.05 were considered significant).

Mice were euthanized when their tumor volume reached the limits described above. One mouse in the CAS-024 treatment group was euthanized on day 45 due to weight loss >20%. This mouse had no apparent SC tumor at that time, and was treated as censored data for the survival analysis (not euthanized as of day 45 due to tumor growth) and was not included in the comparison of tumor-free incidence at the end of the study. No other mice were found dead and none were euthanized due to weight loss, tumor ulceration, or impaired mobility. No overt signs of toxicity or weight loss were observed in any of the treatment groups (data not shown).

The CAS-024 and Rituxan treated mice exhibited a rapid response to treatment. Mean tumor volumes of the CAS-024- and Rituxan®-treated groups were significantly lower than that of the human IgG treated group as early as day 4 (after a single injection of drug) and remained lower through day 11. There were no significant differences in mean tumor volumes or mean relative tumor volumes between the CAS-024 and Rituxan® treated groups through day 11.

The huIgG treated mice were euthanized starting on day 11; therefore, comparisons of tumor volumes were not performed for later time points.

The tumors in the mice treated with huIgG grew rapidly and all mice in this group were euthanized by day 15. In contrast, by day 15, the majority of tumors in the CAS-024 and Rituxan treated groups had regressed to the point that no palpable tumor was present. Notably, the response to treatment was durable only in the CAS-024 treated group. By the end of the study, all of the Rituxan-treated mice were euthanized due to growth of their tumors, whereas 10/14 (71%) of the mice in the CAS-024 treated group remained tumor-free. See Table 9. Thus, at the end of the study, the survival curves and the incidence of tumor-free mice in the CAS-024 treated group differed significantly from the huIgG control group and the Rituxan® treated group. Figure 6 shows that CAS-024 was statistically superior to Rituxan in the *in vivo* treatment of this animal model of follicular lymphoma.

Table 11.

Median Survival Time and Incidence of Tumor-Free Mice

Treatment Group	Treatment Days and Cumulative Dose	Median Survival Time (Days)[a]	p Value from Log Rank Test[b]	Death (other than for Tumor Size Sacrifice)	Tumor-Free Mice at Day 81[c]	Fischer's Exact Test (Comparison of tumor-free incidence)[b]
HuIgG	Days 0, 4, 8 600 μg	13	---	0/15	0/15 (0%)	NA
CAS-024 IP	Days 0, 4, 8 600 μg	**Undefined[d, e]**	<0.0001	1/15[f]	**10/14 (71%)[f]**	<0.0001
Rituxan® IP	Days 0, 4, 8 600 μg	**43**	<0.0001	0/15	0/15 (0%)	NA

[a]"Survival" was determined by the day a mouse was euthanized due to tumor growth. Other than one mouse in the CAS-024 dose group (*see* (f)), no mice were euthanized for reasons other than tumor volume reaching the predetermined limit.

[b]Each group was compared with the HuIgG treated control group.

[c]"Tumor-free" mice had no palpable SC tumors; confirmation of tumor cells absence was not confirmed by histology.

[d]The median survival time is undefined when >50% of the mice are alive at the end of the observation period.

[e]Bold-faced values are significantly different from those of HuIgG control.

[f]One mouse was euthanized on day 45 due to >20% weight loss. The mouse had no apparent SC tumor at that time and was excluded from the group for the comparison of tumor-free mice at day 81.

In conclusion, CAS-024 and Rituxan were efficacious as single agents in a human tumor (DOHH2) xenograft model in SCID mice. While both agents caused an initial tumor regression in the majority of mice, long-term tumor regression was observed only in the group of mice treated with CAS-024 as tumors relapsed after optimal anti-CD20 treatment. Consequently, CAS-024, a humanized anti-CD37 SMIP, shows significant efficacy in pre-clinical tumor xenograft models including models that show that Rituxan® treatment fails over time. These results therefore suggest that CAS-024 treatment of B cell lymphoma and leukemia patients is beneficial and is a viable alternative treatment in patients who fail Rituxan® treatment.

EXAMPLE 9

IN VITRO EVALUATION OF CAS-024 COMBINED WITH CHEMOTHERAPEUTIC AGENTS

It was previously demonstrated that CAS-006 acts synergistically in combination with the chemotherapeutic agent fludarabine to kill chronic lymphocytic leukemia (CLL) cells *in vitro* (*see, e.g.*, US Patent Application Publication No. 2007/0059306). As CLL cells do not actively divide in cell culture *in vitro*, the data indicate that cell proliferation is not required for the pro-apoptotic effect of CAS-006 or CAS-024 for its synergy with chemotherapeutic agents. The purpose of this study, therefore, was to determine whether CAS-024 and various chemotherapeutic agents were effective on a mantle cell lymphoma (MCL) cell line, Rec-1, that actively grows and divides in cell culture *in vitro* and whether the combination of CAS-024 and a chemotherapeutic agent (drug) would desensitize or enhance the response of mantle cell lymphoma cells to various chemotherapeutic agents. The chemotherapeutic agents tested were doxorubicin, vincristine, and fludarabine, which are used to treat non-Hodgkin's lymphoma and other lymphoid malignancies.

Rec-1 cells, a CD37+ human B cell line established from a patient with mantle cell lymphoma, were tested for growth inhibition in response to crosslinked CAS-024 in the presence or absence of doxorubicin, vincristine, or fludarabine (see Figure 7). CAS-024 was preincubated with anti-human IgG

F(ab)'$_2$ to crosslink the protein. Cells were cultured with medium alone or with medium containing various concentrations of the crosslinked CAS-024 protein, in the presence or absence of various concentrations of doxorubicin, vincristine, or fludarabine. Cultures were incubated for 96 hours and growth inhibition was assessed using an ATP viable cell detection system (i.e., viable cells quantified by ATP release).

The Median Effect/ Combination Index (CI) method of Chou and Talalay (Adv. Enzyme Regul. 22:27, 1984) was used for data analysis. A numerical value, assigned to each drug combination at predefined dose levels, enabled quantitative drug/drug interaction comparisons between different drug combinations. Results were expressed as combination indices (CI) vs. effect level, in which effect level represented percent inhibition of cell growth. The mean CI ± SEM for each effect level was averaged over three experiments. A CI < 1.0 was considered synergy, CI = 1.0 additivity, and CI > 1.0 antagonism. Values presented are the mean ± SEM for each effect level, averaging three independent assays.

The combination of CAS-024 with vincristine or fludarabine was synergistic (CI < 1.0) and the combination of CAS-024 and doxorubicin was additive (CI not significantly different from 1.0). None of CAS-024 and chemotherapeutic agent combinations were antagonistic (CI >1.0) across all effect levels. Therefore, the combination of CAS-024 with each of the three chemotherapeutic agents tested did not desensitize target cells to drug-induced growth inhibition, but instead resulted in synergistic or additive inhibitory effects on target cell growth. A preferred embodiment would be the combination of CAS-024 (SEQ ID NO:253) with vincristine or fludarabine. These data indicate that the efficacy of established chemotherapeutics increase when used in combination with CAS-024.

EXAMPLE 10

PRELIMINARY CLINICAL PHASE 1/2 RESULTS

As provided herein, pre-clinical studies have demonstrated that CD37 SMIP molecules mediate significantly greater direct and natural killer (NK)-cell mediated killing of chronic lymphocytic leukemia (CLL) cells as compared to other therapeutic antibodies used in CLL. Hence, a Phase 1/2, open label, dose escalation study has been initiated in patients with relapsed chronic lymphocytic leukemia (CLL).

Patients with relapsed/refractory CLL or small lymphocytic lymphoma (SLL) who had adequate organ function, platelets > 30,000/mm^3 were eligible. Six doses and two different schedules (cohorts 1-10) have/or will be studied. The planned doses range from 0.03 mg/kg to 10 mg/kg IV once a week for 4 doses (cohort 1-6 and 9). The second schedule (cohort 7, 8, and 10) will test 3.0, 6.0, or 10.0 mg/kg on days 1, 3 and 5 the first week followed by 3 weekly doses. Dose escalation and de-escalation is based on Common Toxicity Criteria Adverse Events (CTC AE) toxicity grades. Patients may receive 2 additional cycles, if positive biologic effect after first cycle.

Results: To date, 22 patients have been enrolled (cohort 1-7 and 9) and completed treatment (all have received prior fludarabine and rituximab treatment). Six patients have entered a second cycle and two patients have entered a third cycle. The patients being treated have gone through a number of prior regimens (*e.g.*, Cohort 4 patients had from 6 to 10 (median 6) and Cohort 5 had 5 to 13 (median 9.5) prior regimens). Eight of the ten have high risk genomic features [del(17p13.1), n=5 and del(11q22.3), n=3]. No dose limiting toxicities or serious adverse events have occurred. Mild (grade 1-2) infusion toxicity has been observed in three patients. Beginning with the 0.3 mg/kg dose, all eight patients demonstrated evidence of biological activity including patients with del(17p13.1). Two patients had partial clearing of leukemia cutis, and the median reduction in peripheral lymphocyte count has been 64% (*see* Figure 5). One patient had a 99% reduction in peripheral lymphocyte count with no serious adverse events and a continuing response after 3 months of treatment (*see*

Figure 6). One patient had an increase in hemoglobin of 40% and a reduction in lymph node size of 36% as determined by CT scan and continues to respond after 3 months of treatment (*see* Figure 7). Two patients had a significant increase in platelet count.

Conclusion: To date, this CD37 SMIP molecule is a well tolerated treatment with minimal infusional toxicity and no observed dose limiting toxicity. There also seems to be any complement involvement since patients with severe drops in lymphocyte counts are not showing signs of tumor lysis syndrome. Encouraging reduction in tumor lymphocyte blood counts, reduction in lymph node/spleen size, clearing of leukemia cutis, and/or partial clearing of marrow disease, and/or improvement in normal hematopoeitic function in patients with high risk genomic CLL have already been observed at low, non-saturating doses of CD37 SMIP molecule.

EXAMPLE 11

IN VITRO EFFICACY OF CAS024 COMBINED WITH BENDAMUSTINE

This study was to determine the effects of CAS024, bendamustine, and the combination of CAS024 and bendamustine on Rec-1 (a mantle cell lymphoma cell line) and SU-DHL-6 (a diffuse large cell lymphoma line) cells.

The following human cell lines expressing CD37 were used: Rec-1 and SU-DHL-6 (both from DSMZ, Braunschweig, Germany). Bendamustine (TREANDA®) was purchased from the University of Washington Pharmacy (Seattle, WA) and was dissolved in PBS and stored at -20°C until use.

Rec-1 and SU-DHL-6 cells were plated at $1x10^4$ cells/well in 100 μL medium in 96 well black-sided, black-bottomed plates. Cells were treated with various concentrations of CAS024 that had been preincubated with anti-human IgG F(ab)'$_2$ and plates were incubated for 96 hr at 37°C, 5% CO_2 in the presence of serial dilutions of bendamustine. The final volume in each well was 150 μL. After incubation, plates were cooled to room temperature and labeled with 100 μL/well of ATPlite detection reagent (Perkin Elmer, Boston, MA). The assay measures cellular ATP as a marker for viable cells. Samples were analyzed by

detection of luminescence using a Topcount NXT (Perkin Elmer, Waltham, MA) plate reader. Data were reduced using a 4-parameter curve fit in Prism (version 4.0, Graphpad Software, San Diego, CA) and the IC_{50} defined as the concentration resulting in 50% inhibition compared to untreated cultures.

For synergy determination the Median Effect/ Combination Index (CI) method was used for data analysis (Chou and Talalay). A numerical value, assigned to each drug combination at predefined dose levels, enables quantitative drug/drug interaction comparisons between different drug combinations. The CI values assign interactions into three categories: synergism, additivity, and antagonism (CI<1.0, =1, or >1.0 respectively). After labeling and data reduction, Combination Index (CI) values were determined using the Calcusyn software package (Biosoft, Cambridge, UK). The results of two separate experiments show that the combination of CAS024 with bendamustine resulted in synergistic inhibitory effects on target cell growth (*see*, Figure 11). Similar results were obtained showing that the combination of CAS024 with bendamustine also synergistically inhibited SU-DHL-6 cell growth.

Combination effects of CAS-024 with another alkylating agent, chlorambucil, were also determined using the method described above and the concentrations shown in Figure 12. Unlike bendamustine, chlorambucil in combination with CAS-024 did not result in synergistic inhibitory effects on SU-DHL-6 cell growth (*see*, Figure 13)

EXAMPLE 12

EFFICACY OF CAS024 COMBINED WITH BENDAMUSTINE IN HUMAN TUMOR XENOGRAFT MODEL

This study was to compare the efficacy of CAS024 combined with bendamustine against each agent individually administered against subcutaneous DOHH2 human tumor xenografts in SCID mice.

Establishment of tumor xenografts and sorting into treatment groups. As described above, DOHH2 is a $CD20^{+}CD37^{+}$ human B-lymphoblastoid cell line derived from a patient with follicular lymphoma. Five million DOHH2 cells

were injected subcutaneously into the flank of female CB-17 SCID mice. On day 8 post-tumor inoculation, palpable tumors were apparent in majority of mice. The tumor-bearing mice were sorted into five groups with equivalent mean tumor volumes (n=15 per group; 3 cages of 5 mice for each group). The day of the sort was defined as day 0. Tumor diameters were determined with a pair of calipers and tumor volumes were calculated using the formula: $V=½ [length \times (width)^2]$. The baseline mean tumor volume was 231 mm^3, the median baseline tumor size was 229 mm^3, and the range was 201 to 261 mm^3.

In vivo treatment. Groups of mice were treated with an injection of 0.2 mL of PBS containing 10 µg huIgG (days 0, 4, 8 IV), 10 µg CAS024 (days 0, 4, 8 IV), 10 mg/kg Bendamustine (0, 2, 4, 7, 9 IP), or 10 µg CAS024 (days 0, 4, 8 IV) AND 10 mg/kg Bendamustine (0, 2, 4, 7, 9 IP).

Monitoring and endpoints. Mice were monitored daily by visual inspection. Weights were determined weekly, and tumor diameters were determined at least 3 times per week (M, W, F) by an observer blinded (see above) to the treatment groups. Tumor volumes were calculated as described above.

Mice were euthanized if their tumor volume reached more than 1500 mm^3 (or 1200 mm^3 on Fridays). Death was not an endpoint in this study, and unless noted otherwise, "survival" of a mouse was determined by the time it was euthanized due to its tumor volume reaching the predetermined limits. Mice were euthanized if their tumor volume exceeded the parameters noted above, ulceration of a tumor occurs, the tumor inhibits the mobility of the mouse, or if weight loss exceeds 20%.

Statistical analyses. All statistical analyses were performed using GraphPad Prism software. Significant differences in mean tumor volumes and mean relative tumor volumes were determined using a one-way ANOVA for nonparametric data (Kruskal-Wallis test) with Dunn's multiple comparison post test. Significant differences in survival of mice over time were determined using Kaplan-Meier survival analysis with a log-rank test for comparing survival curves. Significant differences in the incidence of tumor-free mice were determined using Fisher's exact test. p values <0.05 were considered significant.

In the Bendamustine treated groups scruffy coats and diarrhea were seen starting around day 6. On day 10, one mouse in the CAS024 + Bendamustine treatment group was euthanized due to ≥ 20 % weight loss. This mouse was treated as censored data for the analysis of survival curves. No clinical signs of toxicity were seen in the CAS024 alone treatment group.

All treatments, demonstrated an inhibitory effect on the growth of DOHH2 compared to huIgG. On day 13 (which was the last day all mice were alive) the mean tumor volume and mean relative tumor volume of all the treatment groups were statistically different than the huIgG control group of mice (Figures 14A and 4B). A significant difference in mean tumor volumes and mean relative tumor volumes was also seen between Bendamustine and the CAS024 + Bendamustine combination treatment group. There were no significant differences in mean tumor volumes or mean relative tumor volumes between any two other treatment groups. Mean tumor volumes over time of the four groups are shown in Figure 15.

The tumors in the mice treated with huIgG grew rapidly, and all of the mice in this group were euthanized by day 17. As shown in Figure 16 and summarized in Tables 12 and 13, the survival of mice dosed with any of the treatment groups was prolonged compared to the huIgG treated group ($p \leq 0.0001$ for all groups). There was also a significant difference between the survival curves of all three treatment groups and each other with the CAS024/bendamustine combination being superior to either single agent.

None of the huIgG-treated mice were alive (thus none were tumor-free) at the end of the study (day 34) (Figure 17 and Table 12). The incidence of tumor-free mice in the other groups was 0/15 (0%) in the CAS024 and Bendamustine treatment groups and 2/14 (14%) in the CAS024 + Bendamustine combination treatment group. There was no significant difference in the incidence of tumor-free mice between any of the treatment groups.

Table 12. Median Survival Time and Incidence of Tumor-Free Mice at the end of the Observation Period

Treatment Group[a]	Treatment Days	Median Survival Time (Days)[a]	Tumor-Free Incidence at End of Study
huIgG	Days 0, 4, 8	15	0/15 (0%)
CAS024 10 µg	Days 0, 4, 8	**17**[b]	0/15 (0%)
Bendamustine 10 mg/kg	Days 0, 2, 4, 7, 9	**17**	0/15 (0%)
CAS024 + Bendamustine	Days 0, 4, 8 0, 2, 4, 7, 9	**24**	2/14 (14%)[d]

[a] "Survival" of a mouse was determined by the day it was euthanized due to tumor growth. One mouse in the CAS024 + Bendamustine combo group was euthanized on day 10 due to ≥ 20% weight loss. This mouse was treated as censored data when calculating survival curves. No other mice were euthanized for reasons other than its tumor volume reaching the predetermined limit.

[b] Values in bold face indicate that the survival curves of the indicated group are significantly different from those of huIgG control ($p<0.0001$ for all treatment groups; log rank test).

[c] "Tumor-free" mice have no palpable SC tumors. The absence of tumor cells was not confirmed by histology. Study ended on day 34.

[d] In the CAS024 + Bendamustine combo group one mouse was euthanized on day 10 due to ≥ 20% weight loss. No other mice were euthanized for toxicity reasons.

Table 13. p Values for Comparison of Survival Curves Between Treated Groups

p Values for Comparison of survival curves (log- rank test)				
	huIgG	TRU-016	Bendamustine	TRU-016 + Bendamustine
huIgG	NA	**<0.0001**	**<0.0001**	**<0.0001**
TRU-016	**<0.0001** [a]	NA	**0.0050**	**0.01**
Bendamustine	**<0.0001**	**0.0050**	NA	**<0.0001**
TRU-016 + Bendamustine	**<0.0001**	**0.01**	**<0.0001**	NA

This study shows that CAS024 combined with Bendamustine exhibited inhibitory effects on the growth of DOHH2 tumors in SCID mice greater than that seen with either agent alone.

The various embodiments described above can be combined to provide further embodiments. Aspects of the embodiments can be modified, if necessary to employ concepts of the various patents, applications and publications referred to herein to provide yet further embodiments.

These and other changes can be made to the embodiments in light of the above-detailed description. In general, in the following claims, the terms used should not be construed to limit the claims to the specific embodiments disclosed in the specification and the claims, but should be construed to include all possible embodiments along with the full scope of equivalents to which such claims are entitled.

SEQUENCE LISTING

This description contains a sequence listing in electronic form in ASCII text format. A copy of the sequence listing is available from the Canadian Intellectual Property Office. The sequences of SEQ ID NO:1, 2, 5-48, 51, 52, 79-88, 221, 222, 254, and 262-269 are reproduced in the following Table.

SEQUENCE TABLE

<210> 1
<211> 1510
<212> DNA
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 1
aagcttgccg ccatggattt tcaagtgcag attttcagct tcctgctaat cagtgcttca 60
gtcataattg ccagaggagt cgacatccag atgactcagt ctccagcctc cctatctgca 120
tctgtgggag agactgtcac catcacatgt cgaacaagtg aaaatgttta cagttatttg 180
gcttggtatc agcagaaaca gggaaaatct cctcagctcc tggtctcttt tgcaaaaacc 240
ttagcagaag gtgtgccatc aaggttcagt ggcagtggat caggcacaca gttttctctg 300
aagatcagca gcctgcagcc tgaagattct ggaagttatt tctgtcaaca tcattccgat 360
aatccgtgga cgttcggtgg aggcaccgaa ctggagatca aaggtggcgg tggctcgggc 420
ggtggtgggt cgggtggcgg cggatcgtca gcggtccagc tgcagcagtc tggacctgag 480
tcggaaaagc ctggcgcttc agtgaagatt tcctgcaagg cttctggtta ctcattcact 540
ggctacaata tgaactgggt gaagcagaat aatggaaaga gccttgagtg gattggaaat 600
attgatcctt attatggtgg tactacctac aaccggaagt tcaagggcaa ggccacattg 660
actgtagaca aatcctccag cacagcctac atgcagctca agagtctgac atctgaggac 720
tctgcagtct attactgtgc aagatcggtc ggccctatgg actactgggg tcaaggaacc 780
tcagtcaccg tctcttcaga tctggagccc aaatcttctg acaaaactca cacatctcca 840
ccgtgcccag cacctgaact cttgggtgga ccgtcagtct tcctcttccc cccaaaaccc 900
aaggacaccc tcatgatctc ccggacccct gaggtcacat gcgtggtggt ggacgtgagc 960
cacgaagacc ctgaggtcaa gttcaactgg tacgtggacg gcgtggaggt gcataatgcc 1020
aagacaaagc cgcgggagga gcagtacaac agcacgtacc gtgtggtcag cgtcctcacc 1080
gtcctgcacc aggactggct gaatggcaag gagtacaagt gcaaggtctc caacaaagcc 1140
ctcccagccc ccatcgagaa aaccatctcc aaagccaaag ggcagccccg agaaccacag 1200
gtgtacaccc tgcccccatc ccgggatgag ctgaccaaga accaggtcag cctgacctgc 1260
ctggtcaaag gcttctatcc aagcgacatc gccgtggagt gggagagcaa tgggcaaccg 1320
gagaacaact acaagaccac gcctcccgtg ctggactccg acggctcctt cttcctctac 1380
agcaagctca ccgtggacaa gagcaggtgg cagcagggga acgtcttctc atgctccgtg 1440
atgcatgagg ctctgcacaa ccactacacg cagaagagcc tctccctgtc tccgggtaaa 1500
tgagtctaga 1510

<210> 2
<211> 496
<212> PRT
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 2
Met Asp Phe Gln Val Gln Ile Phe Ser Phe Leu Leu Ile Ser Ala Ser
1 5 10 15
Val Ile Ile Ala Arg Gly Val Asp Ile Gln Met Thr Gln Ser Pro Ala
20 25 30

Ser Leu Ser Ala Ser Val Gly Glu Thr Val Thr Ile Thr Cys Arg Thr
35 40 45
Ser Glu Asn Val Tyr Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Gln Gly
50 55 60
Lys Ser Pro Gln Leu Leu Val Ser Phe Ala Lys Thr Leu Ala Glu Gly
65 70 75 80
Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Gln Phe Ser Leu
85 90 95
Lys Ile Ser Ser Leu Gln Pro Glu Asp Ser Gly Ser Tyr Phe Cys Gln
100 105 110
His His Ser Asp Asn Pro Trp Thr Phe Gly Gly Gly Thr Glu Leu Glu
115 120 125
Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
130 135 140
Ser Ser Ala Val Gln Leu Gln Gln Ser Gly Pro Glu Ser Glu Lys Pro
145 150 155 160
Gly Ala Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr
165 170 175
Gly Tyr Asn Met Asn Trp Val Lys Gln Asn Asn Gly Lys Ser Leu Glu
180 185 190
Trp Ile Gly Asn Ile Asp Pro Tyr Tyr Gly Gly Thr Thr Tyr Asn Arg
195 200 205
Lys Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr
210 215 220
Ala Tyr Met Gln Leu Lys Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr
225 230 235 240
Tyr Cys Ala Arg Ser Val Gly Pro Met Asp Tyr Trp Gly Gln Gly Thr
245 250 255
Ser Val Thr Val Ser Ser Asp Leu Glu Pro Lys Ser Ser Asp Lys Thr
260 265 270
His Thr Ser Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
275 280 285
Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
290 295 300
Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
305 310 315 320
Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
325 330 335
Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
340 345 350
Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
355 360 365
Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
370 375 380
Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
385 390 395 400
Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
405 410 415
Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
420 425 430
Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
435 440 445

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
450 455 460
Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
465 470 475 480
Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
485 490 495

<210> 5
<211> 1482
<212> DNA
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 5
atggaagccc cagctcagct tctcttcctc ctgctactct ggctcccaga taccaccgga 60
gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccaggcga aagagccacc 120
ctctcctgcc gaacaagtga aaatgtttac agctacttag cctggtacca acagaaacct 180
ggccaggctc ctaggctcct catctatttt gcaaaaacct tagcagaagg aattccagcc 240
aggttcagtg gcagtggatc cgggacagac ttcactctca ccatcagcag cctagagcct 300
gaagattttg cagtttatta ctgtcaacat cattccgata atccgtggac attcggccaa 360
gggaccaagg tggaaatcaa aggtggcggt ggctcgggcg gtggtggatc tggaggaggt 420
gggaccggtg aggtgcagct ggtgcagtct ggagcagagg tgaaaaagcc cggagagtct 480
ctgaagattt cctgtaaggg atccggttac tcattcactg gctacaatat gaactgggtg 540
cgccagatgc ccgggaaagg cctcgagtgg atgggcaata ttgatcctta ttatggtggt 600
actacctaca accggaagtt caagggccag gtcactatct ccgccgacaa gtccatcagc 660
accgcctacc tgcaatggag cagcctgaag gcctcggaca ccgccatgta ttactgtgca 720
cgctcagtcg gccctatgga ctactggggc cgcggcaccc tggtcactgt ctcctctgat 780
caggagccca aatcttctga caaaactcac acatctccac cgtgcccagc acctgaactc 840
ctgggtggac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc 900
cggacccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag 960
ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag 1020
cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg 1080
aatggcaagg agtacaagtg caaggtctcc aacaaagccc tcccagcccc catcgagaaa 1140
accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gcccccatcc 1200
cgggatgagc tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatcca 1260
agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg 1320
cctcccgtgc tggactccga cggctccttc ttcctctaca gcaagctcac cgtggacaag 1380
agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac 1440
cactacacgc agaagagcct ctccctgtct ccgggtaaat ga 1482

<210> 6
<211> 493
<212> PRT
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 6

Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1 5 10 15
Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser
20 25 30
Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Thr Ser Glu Asn
35 40 45
Val Tyr Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
50 55 60
Arg Leu Leu Ile Tyr Phe Ala Lys Thr Leu Ala Glu Gly Ile Pro Ala
65 70 75 80
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
85 90 95
Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His His Ser
100 105 110
Asp Asn Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Gly
115 120 125
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Thr Gly Glu
130 135 140
Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu Ser
145 150 155 160
Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Gly Tyr Asn
165 170 175
Met Asn Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met Gly
180 185 190
Asn Ile Asp Pro Tyr Tyr Gly Gly Thr Thr Tyr Asn Arg Lys Phe Lys
195 200 205
Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
210 215 220
Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
225 230 235 240
Arg Ser Val Gly Pro Met Asp Tyr Trp Gly Arg Gly Thr Leu Val Thr
245 250 255
Val Ser Ser Asp Gln Glu Pro Lys Ser Ser Asp Lys Thr His Thr Ser
260 265 270
Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
275 280 285
Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
290 295 300
Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
305 310 315 320
Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
325 330 335
Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
340 345 350
Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
355 360 365
Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
370 375 380
Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
385 390 395 400
Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
405 410 415

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
420 425 430
Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
435 440 445
Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
450 455 460
Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
465 470 475 480
His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
485 490

<210> 7
<211> 1482
<212> DNA
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 7
atggaagccc cagctcagct tctcttcctc ctgctactct ggctcccaga taccaccgga 60
gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccaggcga aagagccacc 120
ctctcctgcc gaacaagtga aaatgtttac agctacttag cctggtacca acagaaacct 180
ggccaggctc ctaggctcct catctatttt gcaaaaacct tagcagaagg aattccagcc 240
aggttcagtg gcagtggatc cgggacagac ttcactctca ccatcagcag cctagagcct 300
gaagattttg cagtttatta ctgtcaacat cattccgata atccgtggac attcggccaa 360
gggaccaagg tggaaatcaa aggtggcggt ggctcgggcg gtggtggatc tggaggaggt 420
gggagctctg aggtgcagct ggtgcagtct ggagcagagg tgaaaaagcc cggagagtct 480
ctgaagattt cctgtaaggg atccggttac tcattcactg gctacaatat gaactgggtg 540
cgccagatgc ccgggaaagg cctcgagtgg atgggcaata ttgatcctta ttatggtggt 600
actacctaca accggaagtt caagggccag gtcactatct ccgccgacaa gtccatcagc 660
accgcctacc tgcaatggag cagcctgaag gcctcggaca ccgccatgta ttactgtgca 720
cgctcagtcg gccctatgga ctactggggc cgcggcaccc tggtcactgt ctcctctgat 780
caggagccca aatcttctga caaaactcac acatctccac cgtgcccagc acctgaactc 840
ctgggtggac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc 900
cggacccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag 960
ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag 1020
cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg 1080
aatggcaagg agtacaagtg caaggtctcc aacaaagccc tcccagcccc catcgagaaa 1140
accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gcccccatcc 1200
cgggatgagc tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatcca 1260
agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg 1320
cctcccgtgc tggactccga cggctccttc ttcctctaca gcaagctcac cgtggacaag 1380
agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac 1440
cactacacgc agaagagcct ctccctgtct ccgggtaaat ga 1482

<210> 8
<211> 493
<212> PRT
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 8

Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1 5 10 15
Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser
20 25 30
Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Thr Ser Glu Asn
35 40 45
Val Tyr Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
50 55 60
Arg Leu Leu Ile Tyr Phe Ala Lys Thr Leu Ala Glu Gly Ile Pro Ala
65 70 75 80
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
85 90 95
Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His His Ser
100 105 110
Asp Asn Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Gly
115 120 125
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Glu
130 135 140
Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu Ser
145 150 155 160
Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Gly Tyr Asn
165 170 175
Met Asn Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met Gly
180 185 190
Asn Ile Asp Pro Tyr Tyr Gly Gly Thr Thr Tyr Asn Arg Lys Phe Lys
195 200 205
Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
210 215 220
Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
225 230 235 240
Arg Ser Val Gly Pro Met Asp Tyr Trp Gly Arg Gly Thr Leu Val Thr
245 250 255
Val Ser Ser Asp Gln Glu Pro Lys Ser Ser Asp Lys Thr His Thr Ser
260 265 270
Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
275 280 285
Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
290 295 300
Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
305 310 315 320
Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
325 330 335
Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
340 345 350
Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
355 360 365
Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
370 375 380
Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
385 390 395 400
Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
405 410 415

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
420 425 430
Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
435 440 445
Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
450 455 460
Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
465 470 475 480
His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
485 490

<210> 9
<211> 1482
<212> DNA
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 9
atggaagccc cagctcagct tctcttcctc ctgctactct ggctcccaga taccaccgga 60
gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccaggcga aagagccacc 120
ctctcctgcc gaacaagtga aaatgtttac agctacttag cctggtacca acagaaacct 180
ggccaggctc ctaggctcct catctatttt gcaaaaacct tagcagaagg aattccagcc 240
aggttcagtg gcagtggatc cgggacagac ttcactctca ccatcagcag cctagagcct 300
gaagattttg cagtttatta ctgtcaacat cattccgata atccgtggac attcggccaa 360
gggaccaagg tggaaatcaa aggtggcggt ggctcgggcg gtggtggatc tggaggaggt 420
gggaccggtg aggtgcagct ggtgcagtct ggagcagagt cgaaaaagcc cggagagtct 480
ctgaagattt cctgtaaggg atccggttac tcattcactg gctacaatat gaactgggtg 540
cgccagatgc ccgggaaagg cctcgagtgg atgggcaata ttgatcctta ttatggtggt 600
actacctaca accggaagtt caagggccag gtcactatct ccgccgacaa gtccatcagc 660
accgcctacc tgcaatggag cagcctgaag gcctcggaca ccgccatgta ttactgtgca 720
cgctcagtcg gccctatgga ctactggggc cgcggcaccc tggtcactgt ctcctctgat 780
caggagccca aatcttctga caaaactcac acatctccac cgtgcccagc acctgaactc 840
ctgggtggac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc 900
cggacccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag 960
ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag 1020
cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg 1080
aatggcaagg agtacaagtg caaggtctcc aacaaagccc tcccagcccc catcgagaaa 1140
accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gcccccatcc 1200
cgggatgagc tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatcca 1260
agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg 1320
cctcccgtgc tggactccga cggctccttc ttcctctaca gcaagctcac cgtggacaag 1380
agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac 1440
cactacacgc agaagagcct ctccctgtct ccgggtaaat ga 1482

<210> 10
<211> 493
<212> PRT
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 10

Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1 5 10 15
Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser
20 25 30
Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Thr Ser Glu Asn
35 40 45
Val Tyr Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
50 55 60
Arg Leu Leu Ile Tyr Phe Ala Lys Thr Leu Ala Glu Gly Ile Pro Ala
65 70 75 80
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
85 90 95
Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His His Ser
100 105 110
Asp Asn Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Gly
115 120 125
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Thr Gly Glu
130 135 140
Val Gln Leu Val Gln Ser Gly Ala Glu Ser Lys Lys Pro Gly Glu Ser
145 150 155 160
Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Gly Tyr Asn
165 170 175
Met Asn Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met Gly
180 185 190
Asn Ile Asp Pro Tyr Tyr Gly Gly Thr Thr Tyr Asn Arg Lys Phe Lys
195 200 205
Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
210 215 220
Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
225 230 235 240
Arg Ser Val Gly Pro Met Asp Tyr Trp Gly Arg Gly Thr Leu Val Thr
245 250 255
Val Ser Ser Asp Gln Glu Pro Lys Ser Ser Asp Lys Thr His Thr Ser
260 265 270
Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
275 280 285
Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
290 295 300
Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
305 310 315 320
Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
325 330 335
Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
340 345 350
Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
355 360 365
Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
370 375 380
Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
385 390 395 400
Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
405 410 415

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
420 425 430
Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
435 440 445
Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
450 455 460
Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
465 470 475 480
His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
485 490

<210> 11
<211> 1482
<212> DNA
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 11
atggaagccc cagctcagct tctcttcctc ctgctactct ggctcccaga taccaccgga 60
gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccaggcga aagagccacc 120
ctctcctgcc gaacaagtca aaatgtttac agctacttag cctggtacca acagaaacct 180
ggccaggctc ctaggctcct catctatttt gcaaaaacct tagcagaagg aattccagcc 240
aggttcagtg gcagtggatc cgggacagac ttcactctca ccatcagcag cctagagcct 300
gaagattttg cagtttatta ctgtcaacat cattccgata atccgtggac attcggccaa 360
gggaccaagg tggaaatcaa aggtggcggt ggctcgggcg gtggtggatc tggaggaggt 420
gggaccggtg aggtgcagct ggtgcagtct ggagcagagg tgaaaaagcc cggagagtct 480
ctgaagattt cctgtaaggg atccggttac tcattcactg gctacaatat gaactgggtg 540
cgccagatgc ccgggaaagg cctcgagtgg atgggcaata ttgatcctta ttatggtggt 600
actacctaca accggaagtt caagggccag gtcactatct ccgccgacaa gtccatcagc 660
accgcctacc tgcaatggag cagcctgaag gcctcggaca ccgccatgta ttactgtgca 720
cgctcagtcg gccctatgga ctactggggc cgcggcaccc tggtcactgt ctcctctgat 780
caggagccca aatcttctga caaaactcac acatctccac cgtgcccagc acctgaactc 840
ctgggtggac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc 900
cggacccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag 960
ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag 1020
cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg 1080
aatggcaagg agtacaagtg caaggtctcc aacaaagccc tcccagcccc catcgagaaa 1140
accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gcccccatcc 1200
cgggatgagc tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatcca 1260
agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg 1320
cctcccgtgc tggactccga cggctccttc ttcctctaca gcaagctcac cgtggacaag 1380
agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac 1440
cactacacgc agaagagcct ctccctgtct ccgggtaaat ga 1482

<210> 12
<211> 493
<212> PRT
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 12

Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1 5 10 15
Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser
20 25 30
Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Thr Ser Gln Asn
35 40 45
Val Tyr Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
50 55 60
Arg Leu Leu Ile Tyr Phe Ala Lys Thr Leu Ala Glu Gly Ile Pro Ala
65 70 75 80
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
85 90 95
Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His His Ser
100 105 110
Asp Asn Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Gly
115 120 125
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Thr Gly Glu
130 135 140
Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu Ser
145 150 155 160
Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Gly Tyr Asn
165 170 175
Met Asn Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met Gly
180 185 190
Asn Ile Asp Pro Tyr Tyr Gly Gly Thr Thr Tyr Asn Arg Lys Phe Lys
195 200 205
Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
210 215 220
Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
225 230 235 240
Arg Ser Val Gly Pro Met Asp Tyr Trp Gly Arg Gly Thr Leu Val Thr
245 250 255
Val Ser Ser Asp Gln Glu Pro Lys Ser Ser Asp Lys Thr His Thr Ser
260 265 270
Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
275 280 285
Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
290 295 300
Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
305 310 315 320
Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
325 330 335
Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
340 345 350
Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
355 360 365
Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
370 375 380
Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
385 390 395 400
Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
405 410 415

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
420 425 430
Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
435 440 445
Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
450 455 460
Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
465 470 475 480
His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
485 490

<210> 13
<211> 1482
<212> DNA
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 13
atggaagccc cagctcagct tctcttcctc ctgctactct ggctcccaga taccaccgga 60
gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccaggcga aagagccacc 120
ctctcctgcc gaacaagtga aagtgtttac agctacttag cctggtacca acagaaacct 180
ggccaggctc ctaggctcct catctatttt gcaaaaacct tagcagaagg aattccagcc 240
aggttcagtg gcagtggatc cgggacagac ttcactctca ccatcagcag cctagagcct 300
gaagattttg cagtttatta ctgtcaacat cattccgata atccgtggac attcggccaa 360
gggaccaagg tggaaatcaa aggtggcggt ggctcgggcg gtggtggatc tggaggaggt 420
gggaccggtg aggtgcagct ggtgcagtct ggagcagagg tgaaaaagcc cggagagtct 480
ctgaagattt cctgtaaggg atccggttac tcattcactg gctacaatat gaactgggtg 540
cgccagatgc ccgggaaagg cctcgagtgg atgggcaata ttgatcctta ttatggtggt 600
actacctaca accggaagtt caagggccag gtcactatct ccgccgacaa gtccatcagc 660
accgcctacc tgcaatggag cagcctgaag gcctcggaca ccgccatgta ttactgtgca 720
cgctcagtcg gccctatgga ctactggggc cgcggcaccc tggtcactgt ctcctctgat 780
caggagccca aatcttctga caaaactcac acatctccac cgtgcccagc acctgaactc 840
ctgggtggac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc 900
cggacccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag 960
ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag 1020
cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg 1080
aatggcaagg agtacaagtg caaggtctcc aacaaagccc tcccagcccc catcgagaaa 1140
accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gcccccatcc 1200
cgggatgagc tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatcca 1260
agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg 1320
cctcccgtgc tggactccga cggctccttc ttcctctaca gcaagctcac cgtggacaag 1380
agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac 1440
cactacacgc agaagagcct ctccctgtct ccgggtaaat ga 1482

<210> 14
<211> 493
<212> PRT
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 14

Met	Glu	Ala	Pro	Ala	Gln	Leu	Leu	Phe	Leu	Leu	Leu	Trp	Leu	Pro
1				5				10					15	
Asp	Thr	Thr	Gly	Glu	Ile	Val	Leu	Thr	Gln	Ser	Pro	Ala	Thr	Leu	Ser
			20					25				30		
Leu	Ser	Pro	Gly	Glu	Arg	Ala	Thr	Leu	Ser	Cys	Arg	Thr	Ser	Glu	Ser
		35					40					45			
Val	Tyr	Ser	Tyr	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro
	50					55					60				
Arg	Leu	Leu	Ile	Tyr	Phe	Ala	Lys	Thr	Leu	Ala	Glu	Gly	Ile	Pro	Ala
65					70					75					80
Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser
				85					90					95	
Ser	Leu	Glu	Pro	Glu	Asp	Phe	Ala	Val	Tyr	Tyr	Cys	Gln	His	His	Ser
			100					105				110			
Asp	Asn	Pro	Trp	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys	Gly
		115					120					125			
Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Thr	Gly	Glu
	130					135					140				
Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Glu	Ser
145					150					155					160
Leu	Lys	Ile	Ser	Cys	Lys	Gly	Ser	Gly	Tyr	Ser	Phe	Thr	Gly	Tyr	Asn
				165					170					175	
Met	Asn	Trp	Val	Arg	Gln	Met	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Met	Gly
			180					185					190		
Asn	Ile	Asp	Pro	Tyr	Tyr	Gly	Gly	Thr	Thr	Tyr	Asn	Arg	Lys	Phe	Lys
		195					200					205			
Gly	Gln	Val	Thr	Ile	Ser	Ala	Asp	Lys	Ser	Ile	Ser	Thr	Ala	Tyr	Leu
	210					215					220				
Gln	Trp	Ser	Ser	Leu	Lys	Ala	Ser	Asp	Thr	Ala	Met	Tyr	Tyr	Cys	Ala
225					230					235					240
Arg	Ser	Val	Gly	Pro	Met	Asp	Tyr	Trp	Gly	Arg	Gly	Thr	Leu	Val	Thr
				245					250					255	
Val	Ser	Ser	Asp	Gln	Glu	Pro	Lys	Ser	Ser	Asp	Lys	Thr	His	Thr	Ser
			260					265					270		
Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu
		275					280					285			
Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu
	290					295					300				
Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys
305					310					315					320
Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys
				325					330					335	
Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu
			340					345					350		
Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys
		355					360					365			
Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys
	370					375					380				
Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser
385					390					395					400
Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys
				405					410					415	

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
420 425 430
Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
435 440 445
Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
450 455 460
Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
465 470 475 480
His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
485 490

<210> 15
<211> 1482
<212> DNA
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 15
atggaagccc cagctcagct tctcttcctc ctgctactct ggctcccaga taccaccgga 60
gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccaggcga aagagccacc 120
ctctcctgcc gagcaagtga aaatgtttac agctacttag cctggtacca acagaaacct 180
ggccaggctc ctaggctcct catctatttt gcaaaaacct tagcagaagg aattccagcc 240
aggttcagtg gcagtggatc cgggacagac ttcactctca ccatcagcag cctagagcct 300
gaagattttg cagtttatta ctgtcaacat cattccgata atccgtggac attcggccaa 360
gggaccaagg tggaaatcaa aggtggcggt ggctcgggcg gtggtggatc tggaggaggt 420
gggaccggtg aggtgcagct ggtgcagtct ggagcagagg tgaaaaagcc cggagagtct 480
ctgaagattt cctgtaaggg atccggttac tcattcactg gctacaatat gaactgggtg 540
cgccagatgc ccgggaaagg cctcgagtgg atgggcaata ttgatcctta ttatggtggt 600
actacctaca accggaagtt caagggccag gtcactatct ccgccgacaa gtccatcagc 660
accgcctacc tgcaatggag cagcctgaag gcctcggaca ccgccatgta ttactgtgca 720
cgctcagtcg gccctatgga ctactggggc cgcggcaccc tggtcactgt ctcctctgat 780
caggagccca aatcttctga caaaactcac acatctccac cgtgcccagc acctgaactc 840
ctgggtggac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc 900
cggacccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag 960
ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag 1020
cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg 1080
aatggcaagg agtacaagtg caaggtctcc aacaaagccc tcccagcccc catcgagaaa 1140
accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gcccccatcc 1200
cgggatgagc tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatcca 1260
agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg 1320
cctcccgtgc tggactccga cggctccttc ttcctctaca gcaagctcac cgtggacaag 1380
agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac 1440
cactacacgc agaagagcct ctccctgtct ccgggtaaat ga 1482

<210> 16
<211> 493
<212> PRT
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 16

Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1 5 10 15
Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser
20 25 30
Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Glu Asn
35 40 45
Val Tyr Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
50 55 60
Arg Leu Leu Ile Tyr Phe Ala Lys Thr Leu Ala Glu Gly Ile Pro Ala
65 70 75 80
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
85 90 95
Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His His Ser
100 105 110
Asp Asn Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Gly
115 120 125
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Thr Gly Glu
130 135 140
Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu Ser
145 150 155 160
Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Gly Tyr Asn
165 170 175
Met Asn Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met Gly
180 185 190
Asn Ile Asp Pro Tyr Tyr Gly Gly Thr Thr Tyr Asn Arg Lys Phe Lys
195 200 205
Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
210 215 220
Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
225 230 235 240
Arg Ser Val Gly Pro Met Asp Tyr Trp Gly Arg Gly Thr Leu Val Thr
245 250 255
Val Ser Ser Asp Gln Glu Pro Lys Ser Ser Asp Lys Thr His Thr Ser
260 265 270
Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
275 280 285
Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
290 295 300
Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
305 310 315 320
Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
325 330 335
Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
340 345 350
Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
355 360 365
Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
370 375 380
Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
385 390 395 400
Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
405 410 415

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
420 425 430
Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
435 440 445
Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
450 455 460
Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
465 470 475 480
His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
485 490

<210> 17
<211> 1479
<212> DNA
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 17
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt 60
gacatccaga tgactcagtc tccagcctcc ctatctgcat ctgtgggaga gactgtcacc 120
atcacatgtc gaacaagtga aaatgtttac agttatttgg cttggtatca gcagaaacag 180
ggaaaatctc ctcagctcct ggtctctttt gcaaaaacct tagcagaagg tgtgccatca 240
aggttcagtg gcagtggatc aggcacacag ttttctctga agatcagcag cctgcagcct 300
gaagattctg gaagttattt ctgtcaacat cattccgata atccgtggac gttcggtgga 360
ggcaccgaac tggagatcaa aggtggcggt ggctcgggcg gtggtgggtc gggtggcggc 420
ggagctagcg aggtgcagct ggtgcagtct ggagcagagg tgaaaaagcc cggagagtct 480
ctgaggattt cctgtaaggg atccggttac tcattcactg gctacaatat gaactgggtg 540
cgccagatgc ccgggaaagg cctggagtgg atgggcaata ttgatcctta ttatggtggt 600
actacctaca accggaagtt caagggccag gtcactatct ccgccgacaa gtccatcagc 660
accgcctacc tgcaatggag cagcctgaag gcctcggaca ccgccatgta ttactgtgca 720
cgctcagtcg gccctatgga ctactggggc cgcggcaccc tggtcactgt ctcctcgagc 780
gagcccaaat cttctgacaa aactcacaca tctccaccgt gcccagcacc tgaactcctg 840
ggtggaccgt cagtcttcct cttccccccа aaacccaagg acaccctcat gatctcccgg 900
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc 960
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag 1020
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat 1080
ggcaaggagt acaagtgcaa ggtctccaac aaagccctcc cagccccccat cgagaaaacc 1140
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg 1200
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc 1260
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct 1320
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc 1380
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac 1440
tacacgcaga agagcctctc cctgtctccg ggtaaatga 1479

<210> 18
<211> 492
<212> PRT
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 18

Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1 5 10 15
Asp Thr Thr Gly Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser
20 25 30
Ala Ser Val Gly Glu Thr Val Thr Ile Thr Cys Arg Thr Ser Glu Asn
35 40 45
Val Tyr Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Gln Gly Lys Ser Pro
50 55 60
Gln Leu Leu Val Ser Phe Ala Lys Thr Leu Ala Glu Gly Val Pro Ser
65 70 75 80
Arg Phe Ser Gly Ser Gly Ser Gly Thr Gln Phe Ser Leu Lys Ile Ser
85 90 95
Ser Leu Gln Pro Glu Asp Ser Gly Ser Tyr Phe Cys Gln His His Ser
100 105 110
Asp Asn Pro Trp Thr Phe Gly Gly Gly Thr Glu Leu Glu Ile Lys Gly
115 120 125
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ala Ser Glu
130 135 140
Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu Ser
145 150 155 160
Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Gly Tyr Asn
165 170 175
Met Asn Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met Gly
180 185 190
Asn Ile Asp Pro Tyr Tyr Gly Gly Thr Thr Tyr Asn Arg Lys Phe Lys
195 200 205
Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
210 215 220
Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
225 230 235 240
Arg Ser Val Gly Pro Met Asp Tyr Trp Gly Arg Gly Thr Leu Val Thr
245 250 255
Val Ser Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr His Thr Ser Pro
260 265 270
Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
275 280 285
Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
290 295 300
Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
305 310 315 320
Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
325 330 335
Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
340 345 350
Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
355 360 365
Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
370 375 380
Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
385 390 395 400
Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
405 410 415

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
420 425 430
Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
435 440 445
Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
450 455 460
Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
465 470 475 480
Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
485 490

<210> 19
<211> 1479
<212> DNA
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 19
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt 60
gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccaggcga aagagccacc 120
ctctcctgcc gaacaagtga aaatgtttac agctacttag cctggtacca acagaaacct 180
ggccaggctc ctaggctcct catctatttt gcaaaaacct tagcagaagg aattccagcc 240
aggttcagtg gcagtggatc cgggacagac ttcactctca ccatcagcag cctagagcct 300
gaagattttg cagtttatta ctgtcaacat cattccgata atccgtggac attcggccaa 360
gggaccaagg tggaaatcaa aggtggcggt ggctcgggcg gtagtggatc tggaggaggt 420
ggagctagcg cggtccagct gcagcagtct ggacctgagt cggaaaagcc tggcgcttca 480
gtgaagattt cctgcaaggc ttctggttac tcattcactg gctacaatat gaactgggtg 540
aagcagaata atggaaagag ccttgagtgg attggaaata ttgatcctta ttatggtggt 600
actacctaca accggaagtt caagggcaag gccacattga ctgtagacaa atcctccagc 660
acagcctaca tgcagctcaa gagtctgaca tctgaggact ctgcagtcta ttactgtgca 720
agatcggtcg gccctatgga ctactggggt caaggaacct cagtcaccgt ctcctcgagc 780
gagcccaaat cttctgacaa aactcacaca tctccaccgt gcccagcacc tgaactcctg 840
ggtggaccgt cagtcttcct cttccccccа aaacccaagg acaccctcat gatctcccgg 900
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc 960
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag 1020
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat 1080
ggcaaggagt acaagtgcaa ggtctccaac aaagccctcc cagccccccat cgagaaaacc 1140
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg 1200
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc 1260
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct 1320
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc 1380
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac 1440
tacacgcaga agagcctctc cctgtctccg ggtaaatga 1479

<210> 20
<211> 492
<212> PRT
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 20

Met	Glu	Ala	Pro	Ala	Gln	Leu	Leu	Phe	Leu	Leu	Leu	Leu	Trp	Leu	Pro
1				5				10						15	
Asp	Thr	Thr	Gly	Glu	Ile	Val	Leu	Thr	Gln	Ser	Pro	Ala	Thr	Leu	Ser
			20					25					30		
Leu	Ser	Pro	Gly	Glu	Arg	Ala	Thr	Leu	Ser	Cys	Arg	Thr	Ser	Glu	Asn
		35					40					45			
Val	Tyr	Ser	Tyr	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro
	50					55					60				
Arg	Leu	Leu	Ile	Tyr	Phe	Ala	Lys	Thr	Leu	Ala	Glu	Gly	Ile	Pro	Ala
65					70					75					80
Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser
				85					90					95	
Ser	Leu	Glu	Pro	Glu	Asp	Phe	Ala	Val	Tyr	Tyr	Cys	Gln	His	His	Ser
			100					105					110		
Asp	Asn	Pro	Trp	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys	Gly
		115					120					125			
Gly	Gly	Gly	Ser	Gly	Gly	Ser	Gly	Ser	Gly	Gly	Gly	Gly	Ala	Ser	Ala
	130					135					140				
Val	Gln	Leu	Gln	Gln	Ser	Gly	Pro	Glu	Ser	Glu	Lys	Pro	Gly	Ala	Ser
145					150					155					160
Val	Lys	Ile	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Ser	Phe	Thr	Gly	Tyr	Asn
				165					170					175	
Met	Asn	Trp	Val	Lys	Gln	Asn	Asn	Gly	Lys	Ser	Leu	Glu	Trp	Ile	Gly
			180					185					190		
Asn	Ile	Asp	Pro	Tyr	Tyr	Gly	Gly	Thr	Thr	Tyr	Asn	Arg	Lys	Phe	Lys
		195					200					205			
Gly	Lys	Ala	Thr	Leu	Thr	Val	Asp	Lys	Ser	Ser	Ser	Thr	Ala	Tyr	Met
	210					215					220				
Gln	Leu	Lys	Ser	Leu	Thr	Ser	Glu	Asp	Ser	Ala	Val	Tyr	Tyr	Cys	Ala
225					230					235					240
Arg	Ser	Val	Gly	Pro	Met	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Ser	Val	Thr
				245					250					255	
Val	Ser	Ser	Ser	Glu	Pro	Lys	Ser	Ser	Asp	Lys	Thr	His	Thr	Ser	Pro
			260					265					270		
Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe
		275					280					285			
Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val
	290					295					300				
Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe
305					310					315					320
Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro
				325					330					335	
Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr
			340					345					350		
Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val
		355					360					365			
Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala
	370					375					380				
Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg
385					390					395					400
Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly
				405					410					415	

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
420 425 430
Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
435 440 445
Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
450 455 460
Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
465 470 475 480
Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
485 490

<210> 21
<211> 1479
<212> DNA
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 21
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt 60
gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccaggcga aagagccacc 120
ctctcctgcc gaacaagtga aaatgtttac agctacttag cctggtacca acagaaacct 180
ggccaggctc ctaggctcct catctatttt gcaaaaacct tagcagaagg aattccagcc 240
aggttcagtg gcagtggatc cgggacagac ttcactctca ccatcagcag cctagagcct 300
gaagattttg cagtttatta ctgtcaacat cattccgata atccgtggac attcggccaa 360
gggaccaagg tggaaatcaa aggtggcggt ggctcgggcg gtggtggatc tggaggaggt 420
ggagctagcc aggtgcagct ggtggagtct ggtggaggcg tggtccagcc tgggaggtcc 480
ctgagactct cctgtgcagc ctctggattc accttcagtg gctacaatat gaactgggtc 540
cgccagatgc ccgggaaagg cctggagtgg atgggcaata ttgatcctta ttatggtggt 600
actacctaca accggaagtt caagggccag gtcactatct ccgccgacaa gtccatcagc 660
accgcctacc tgcaatggag cagcctgaag gcctcggaca ccgccatgta ttactgtgca 720
cgctcagtcg gccctatgga ctactggggc cgcggcaccc tggtcactgt ctcctcgagc 780
gagcccaaat cttctgacaa aactcacaca tctccaccgt gcccagcacc tgaactcctg 840
ggtggaccgt cagtcttcct cttccccccа aaacccaagg acaccctcat gatctcccgg 900
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc 960
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag 1020
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat 1080
ggcaaggagt acaagtgcaa ggtctccaac aaagccctcc cagccccccat cgagaaaacc 1140
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg 1200
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc 1260
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct 1320
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc 1380
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac 1440
tacacgcaga agagcctctc cctgtctccg ggtaaatga 1479

<210> 22
<211> 492
<212> PRT
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 22

Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1 5 10 15
Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser
20 25 30
Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Thr Ser Glu Asn
35 40 45
Val Tyr Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
50 55 60
Arg Leu Leu Ile Tyr Phe Ala Lys Thr Leu Ala Glu Gly Ile Pro Ala
65 70 75 80
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
85 90 95
Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His His Ser
100 105 110
Asp Asn Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Gly
115 120 125
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ala Ser Gln
130 135 140
Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg Ser
145 150 155 160
Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Gly Tyr Asn
165 170 175
Met Asn Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met Gly
180 185 190
Asn Ile Asp Pro Tyr Tyr Gly Gly Thr Thr Tyr Asn Arg Lys Phe Lys
195 200 205
Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
210 215 220
Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
225 230 235 240
Arg Ser Val Gly Pro Met Asp Tyr Trp Gly Arg Gly Thr Leu Val Thr
245 250 255
Val Ser Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr His Thr Ser Pro
260 265 270
Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
275 280 285
Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
290 295 300
Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
305 310 315 320
Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
325 330 335
Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
340 345 350
Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
355 360 365
Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
370 375 380
Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
385 390 395 400
Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
405 410 415

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
420 425 430
Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
435 440 445
Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
450 455 460
Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
465 470 475 480
Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
485 490

<210> 23
<211> 1503
<212> DNA
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 23
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt 60
gcggtccagc tgcagcagtc tggacctgag tcggaaaagc ctggcgcttc agtgaagatt 120
tcctgcaagg cttctggtta ctcattcact ggctacaata tgaactgggt gaagcagaat 180
aatggaaaga gccttgagtg gattggaaat attgatcctt attatggtgg tactacctac 240
aaccggaagt tcaagggcaa ggccacattg actgtagaca aatcctccag cacagcctac 300
atgcagctca agagtctgac atctgaggac tctgcagtct attactgtgc aagatcggtc 360
ggccctatgg actactgggg tcaaggaacc tcagtcaccg tctcttctgg tggcggtggc 420
tcgggcggtg gtgggtcggg tggcggcgga tcaggaggag gcgggagtgc tagcgaaatt 480
gtgttgacac agtctccagc caccctgtct ttgtctccag gcgaaagagc caccctctcc 540
tgccgaacaa gtgaaaatgt ttacagctac ttagcctggt accaacagaa acctggccag 600
gctcctaggc tcctcatcta ttttgcaaaa accttagcag aaggaattcc agccaggttc 660
agtggcagtg gatccgggac agacttcact ctcaccatca gcagcctaga gcctgaagat 720
tttgcagttt attactgtca acatcattcc gataatccgt ggacattcgg ccaagggacc 780
aaggtggaaa tcaaaggctc gagcgagccc aaatcttctg acaaaactca cacatctcca 840
ccgtgcccag cacctgaact cctgggtgga ccgtcagtct tcctcttccc cccaaaaccc 900
aaggacaccc tcatgatctc ccggacccct gaggtcacat gcgtggtggt ggacgtgagc 960
cacgaagacc ctgaggtcaa gttcaactgg tacgtggacg gcgtggaggt gcataatgcc 1020
aagacaaagc cgcgggagga gcagtacaac agcacgtacc gtgtggtcag cgtcctcacc 1080
gtcctgcacc aggactggct gaatggcaag gagtacaagt gcaaggtctc caacaaagcc 1140
ctcccagccc ccatcgagaa aaccatctcc aaagccaaag ggcagccccg agaaccacag 1200
gtgtacaccc tgcccccatc ccgggatgag ctgaccaaga accaggtcag cctgacctgc 1260
ctggtcaaag gcttctatcc aagcgacatc gccgtggagt gggagagcaa tgggcagccg 1320
gagaacaact acaagaccac gcctcccgtg ctggactccg acggctcctt cttcctctac 1380
agcaagctca ccgtggacaa gagcaggtgg cagcagggga acgtcttctc atgctccgtg 1440
atgcatgagg ctctgcacaa ccactacacg cagaagagcc tctccctgtc tccgggtaaa 1500
tga 1503

<210> 24
<211> 500
<212> PRT
<213> Artificial sequence

<220>

<223> CD37 specific binding protein

<400> 24

Met	Glu	Ala	Pro	Ala	Gln	Leu	Leu	Phe	Leu	Leu	Leu	Leu	Trp	Leu	Pro
1				5				10						15	
Asp	Thr	Thr	Gly	Ala	Val	Gln	Leu	Gln	Gln	Ser	Gly	Pro	Glu	Ser	Glu
			20					25					30		
Lys	Pro	Gly	Ala	Ser	Val	Lys	Ile	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Ser
		35					40					45			
Phe	Thr	Gly	Tyr	Asn	Met	Asn	Trp	Val	Lys	Gln	Asn	Asn	Gly	Lys	Ser
	50					55					60				
Leu	Glu	Trp	Ile	Gly	Asn	Ile	Asp	Pro	Tyr	Tyr	Gly	Gly	Thr	Thr	Tyr
65					70					75					80
Asn	Arg	Lys	Phe	Lys	Gly	Lys	Ala	Thr	Leu	Thr	Val	Asp	Lys	Ser	Ser
				85					90					95	
Ser	Thr	Ala	Tyr	Met	Gln	Leu	Lys	Ser	Leu	Thr	Ser	Glu	Asp	Ser	Ala
			100					105					110		
Val	Tyr	Tyr	Cys	Ala	Arg	Ser	Val	Gly	Pro	Met	Asp	Tyr	Trp	Gly	Gln
		115					120					125			
Gly	Thr	Ser	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly
	130					135					140				
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Ala	Ser	Glu	Ile
145					150					155					160
Val	Leu	Thr	Gln	Ser	Pro	Ala	Thr	Leu	Ser	Leu	Ser	Pro	Gly	Glu	Arg
				165					170					175	
Ala	Thr	Leu	Ser	Cys	Arg	Thr	Ser	Glu	Asn	Val	Tyr	Ser	Tyr	Leu	Ala
			180					185					190		
Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Leu	Leu	Ile	Tyr	Phe
		195					200					205			
Ala	Lys	Thr	Leu	Ala	Glu	Gly	Ile	Pro	Ala	Arg	Phe	Ser	Gly	Ser	Gly
	210					215					220				
Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Glu	Pro	Glu	Asp
225					230					235					240
Phe	Ala	Val	Tyr	Tyr	Cys	Gln	His	His	Ser	Asp	Asn	Pro	Trp	Thr	Phe
				245					250					255	
Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys	Gly	Ser	Ser	Glu	Pro	Lys	Ser
			260					265					270		
Ser	Asp	Lys	Thr	His	Thr	Ser	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu
		275					280					285			
Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu
	290					295					300				
Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser
305					310					315					320
His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu
				325					330					335	
Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr
			340					345					350		
Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn
		355					360					365			
Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro
	370					375					380				
Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln
385					390					395					400

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
405 410 415
Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
420 425 430
Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
435 440 445
Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
450 455 460
Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
465 470 475 480
Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
485 490 495
Ser Pro Gly Lys
500

<210> 25
<211> 1488
<212> DNA
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 25
atggattttc aagtgcagat tttcagcttc ctgctaatca gtgcttcagt cataattgcc 60
agaggagtcg aaattgtgtt gacacagtct ccagccaccc tgtctttgtc tccaggcgaa 120
agagccaccc tctcctgccg aacaagtgaa aatgtttaca gctacttagc ctggtaccaa 180
cagaaacctg gccaggctcc taggctcctc atctattttg caaaaacctt agcagaagga 240
attccagcca ggttcagtgg cagtggatcc gggacagact tcactctcac catcagcagc 300
ctagagcctg aagattttgc agtttattac tgtcaacatc attccgataa tccgtggaca 360
ttcggccaag ggaccaaggt ggaaatcaaa ggtggcggtg gctcgggcgg tggtggatct 420
ggaggaggtg gagctagcgc ggtccagctg cagcagtctg gacctgagtc ggaaaagcct 480
ggcgcttcag tgaagatttc ctgcaaggct tctggttact cattcactgg ctacaatatg 540
aactgggtga agcagaataa tggaaagagc cttgagtgga ttggaaatat tgatccttat 600
tatggtggta ctacctacaa ccggaagttc aagggcaagg ccacattgac tgtagacaaa 660
tcctccagca cagcctacat gcagctcaag agtctgacat ctgaggactc tgcagtctat 720
tactgtgcaa gatcggtcgg ccctatggac tactggggtc aaggaacctc agtcaccgtc 780
tcctcgagcg agcccaaatc ttctgacaaa actcacacat ctccaccgtg cccagcacct 840
gaactcctgg gtggaccgtc agtcttcctc ttccccccaa aacccaagga caccctcatg 900
atctcccgga ccctgaggt cacatgcgtg gtggtggacg tgagccacga agaccctgag 960
gtcaagttca actggtacgt ggacggcgtg gaggtgcata atgccaagac aaagccgcgg 1020
gaggagcagt acaacagcac gtaccgtgtg gtcagcgtcc tcaccgtcct gcaccaggac 1080
tggctgaatg gcaaggagta caagtgcaag gtctccaaca aagccctccc agcccccatc 1140
gagaaaacca tctccaaagc caaagggcag ccccgagaac cacaggtgta caccctgccc 1200
ccatcccggg atgagctgac caagaaccag gtcagcctga cctgcctggt caaaggcttc 1260
tatccaagcg acatcgccgt ggagtgggag agcaatgggc agccggagaa caactacaag 1320
accacgcctc ccgtgctgga ctccgacggc tccttcttcc tctacagcaa gctcaccgtg 1380
gacaagagca ggtggcagca ggggaacgtc ttctcatgct ccgtgatgca tgaggctctg 1440
cacaaccact acacgcagaa gagcctctcc ctgtctccgg gtaaatga 1488

<210> 26
<211> 495
<212> PRT

<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 26

Met	Asp	Phe	Gln	Val	Gln	Ile	Phe	Ser	Phe	Leu	Leu	Ile	Ser	Ala	Ser
1				5				10						15	
Val	Ile	Ile	Ala	Arg	Gly	Val	Glu	Ile	Val	Leu	Thr	Gln	Ser	Pro	Ala
			20					25					30		
Thr	Leu	Ser	Leu	Ser	Pro	Gly	Glu	Arg	Ala	Thr	Leu	Ser	Cys	Arg	Thr
		35					40					45			
Ser	Glu	Asn	Val	Tyr	Ser	Tyr	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly
	50					55					60				
Gln	Ala	Pro	Arg	Leu	Leu	Ile	Tyr	Phe	Ala	Lys	Thr	Leu	Ala	Glu	Gly
65					70					75					80
Ile	Pro	Ala	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu
				85					90					95	
Thr	Ile	Ser	Ser	Leu	Glu	Pro	Glu	Asp	Phe	Ala	Val	Tyr	Tyr	Cys	Gln
			100					105					110		
His	His	Ser	Asp	Asn	Pro	Trp	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu
		115					120					125			
Ile	Lys	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly
	130					135					140				
Ala	Ser	Ala	Val	Gln	Leu	Gln	Gln	Ser	Gly	Pro	Glu	Ser	Glu	Lys	Pro
145					150					155					160
Gly	Ala	Ser	Val	Lys	Ile	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Ser	Phe	Thr
				165					170					175	
Gly	Tyr	Asn	Met	Asn	Trp	Val	Lys	Gln	Asn	Asn	Gly	Lys	Ser	Leu	Glu
			180					185					190		
Trp	Ile	Gly	Asn	Ile	Asp	Pro	Tyr	Tyr	Gly	Gly	Thr	Thr	Tyr	Asn	Arg
		195					200					205			
Lys	Phe	Lys	Gly	Lys	Ala	Thr	Leu	Thr	Val	Asp	Lys	Ser	Ser	Ser	Thr
	210					215					220				
Ala	Tyr	Met	Gln	Leu	Lys	Ser	Leu	Thr	Ser	Glu	Asp	Ser	Ala	Val	Tyr
225					230					235					240
Tyr	Cys	Ala	Arg	Ser	Val	Gly	Pro	Met	Asp	Tyr	Trp	Gly	Gln	Gly	Thr
				245					250					255	
Ser	Val	Thr	Val	Ser	Ser	Ser	Glu	Pro	Lys	Ser	Ser	Asp	Lys	Thr	His
			260					265					270		
Thr	Ser	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val
		275					280					285			
Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr
	290					295					300				
Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu
305					310					315					320
Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys
				325					330					335	
Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser
			340					345					350		
Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys
		355					360					365			

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
370 375 380
Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
385 390 395 400
Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
405 410 415
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
420 425 430
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
435 440 445
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
450 455 460
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
465 470 475 480
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
485 490 495

<210> 27
<211> 1503
<212> DNA
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 27
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt 60
gcggtccagc tgcagcagtc tggacctgag tcggaaaagc ctggcgcttc agtgaagatt 120
tcctgcaagg cttctggtta ctcattcact ggctacaata tgaactgggt gaagcagaat 180
aatggaaaga gccttgagtg gattggaaat attgatcctt attatggtgg tactacctac 240
aaccggaagt tcaagggcaa ggccacattg actgtagaca aatcctccag cacagcctac 300
atgcagctca agagtctgac atctgaggac tctgcagtct attactgtgc aagatcggtc 360
ggccctatgg actactgggg tcaaggaacc tcagtcaccg tctcttctgg tggcggtggc 420
tcgggcggtg gtgggtcggg tggcggcgga tcaggaggag gcgggagtgc tagcgaaatt 480
gtgttgacac agtctccagc caccctgtct ttgtctccag gcgaaagagc caccctctcc 540
tgccgaacaa gtgaaaatgt ttacagctac ttagcctggt accaacagaa acctggccag 600
gctcctaggc tcctcatcta ttttgcaaaa accttagcag aaggaattcc agccaggttc 660
agtggcagtg gatccgggac agacttcact ctcaccatca gcagcctaga gcctgaagat 720
tttgcagttt attactgtca acatcattcc gataatccgt ggacattcgg ccaagggacc 780
aaggtggaaa tcaaaggctc gagcgagccc aaatcttctg acaaaactca cacatgccca 840
ccgtgcccag cacctgaact cctgggtgga ccgtcagtct tcctcttccc cccaaaaccc 900
aaggacaccc tcatgatctc ccggacccct gaggtcacat gcgtggtggt ggacgtgagc 960
cacgaagacc ctgaggtcaa gttcaactgg tacgtggacg gcgtggaggt gcataatgcc 1020
aagacaaagc cgcgggagga gcagtacaac agcacgtacc gtgtggtcag cgtcctcacc 1080
gtcctgcacc aggactggct gaatggcaag gagtacaagt gcaaggtctc caacaaagcc 1140
ctcccagccc ccatcgagaa aaccatctcc aaagccaaag ggcagccccg agaaccacag 1200
gtgtacaccc tgcccccatc ccgggatgag ctgaccaaga accaggtcag cctgacctgc 1260
ctggtcaaag gcttctatcc aagcgacatc gccgtggagt gggagagcaa tgggcagccg 1320
gagaacaact acaagaccac gcctcccgtg ctggactccg acggctcctt cttcctctac 1380
agcaagctca ccgtggacaa gagcaggtgg cagcagggga acgtcttctc atgctccgtg 1440
atgcatgagg ctctgcacaa ccactacacg cagaagagcc tctccctgtc tccgggtaaa 1500
tga 1503

<210> 28
<211> 500
<212> PRT
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 28

Met	Glu	Ala	Pro	Ala	Gln	Leu	Leu	Phe	Leu	Leu	Leu	Leu	Trp	Leu	Pro
1				5				10					15		
Asp	Thr	Thr	Gly	Ala	Val	Gln	Leu	Gln	Gln	Ser	Gly	Pro	Glu	Ser	Glu
			20					25					30		
Lys	Pro	Gly	Ala	Ser	Val	Lys	Ile	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Ser
		35					40					45			
Phe	Thr	Gly	Tyr	Asn	Met	Asn	Trp	Val	Lys	Gln	Asn	Asn	Gly	Lys	Ser
	50					55					60				
Leu	Glu	Trp	Ile	Gly	Asn	Ile	Asp	Pro	Tyr	Tyr	Gly	Gly	Thr	Thr	Tyr
65					70					75					80
Asn	Arg	Lys	Phe	Lys	Gly	Lys	Ala	Thr	Leu	Thr	Val	Asp	Lys	Ser	Ser
				85					90					95	
Ser	Thr	Ala	Tyr	Met	Gln	Leu	Lys	Ser	Leu	Thr	Ser	Glu	Asp	Ser	Ala
			100					105					110		
Val	Tyr	Tyr	Cys	Ala	Arg	Ser	Val	Gly	Pro	Met	Asp	Tyr	Trp	Gly	Gln
		115					120					125			
Gly	Thr	Ser	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly
	130					135					140				
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Ala	Ser	Glu	Ile
145					150					155					160
Val	Leu	Thr	Gln	Ser	Pro	Ala	Thr	Leu	Ser	Leu	Ser	Pro	Gly	Glu	Arg
				165					170					175	
Ala	Thr	Leu	Ser	Cys	Arg	Thr	Ser	Glu	Asn	Val	Tyr	Ser	Tyr	Leu	Ala
			180					185					190		
Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Leu	Leu	Ile	Tyr	Phe
		195					200					205			
Ala	Lys	Thr	Leu	Ala	Glu	Gly	Ile	Pro	Ala	Arg	Phe	Ser	Gly	Ser	Gly
	210					215					220				
Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Glu	Pro	Glu	Asp
225					230					235					240
Phe	Ala	Val	Tyr	Tyr	Cys	Gln	His	His	Ser	Asp	Asn	Pro	Trp	Thr	Phe
				245					250					255	
Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys	Gly	Ser	Ser	Glu	Pro	Lys	Ser
			260					265					270		
Ser	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu
		275					280					285			
Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu
	290					295					300				
Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser
305					310					315					320
His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu
				325					330					335	
Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr
			340					345					350		

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
355 360 365
Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
370 375 380
Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
385 390 395 400
Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
405 410 415
Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
420 425 430
Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
435 440 445
Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
450 455 460
Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
465 470 475 480
Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
485 490 495
Ser Pro Gly Lys
500

<210> 29
<211> 1479
<212> DNA
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 29
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt 60
gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccaggcga aagagccacc 120
ctctcctgcc gaacaagtga aaatgtttac agctacttag cctggtacca acagaaacct 180
ggccaggctc ctaggctcct catctatttt gcaaaaacct tagcagaagg aattccagcc 240
aggttcagtg gcagtggatc cgggacagac ttcactctca ccatcagcag cctagagcct 300
gaagattttg cagtttatta ctgtcaacat cattccgata atccgtggac attcggccaa 360
gggaccaagg tggaaatcaa aggtggcggt ggctcgggcg gtggtggatc tggaggaggt 420
ggagctagcg cggtccagct gcagcagtct ggacctgagt cggaaaagcc tggcgcttca 480
gtgaagattt cctgcaaggc ttctggttac tcattcactg gctacaatat gaactgggtg 540
aagcagaata atggaaagag ccttgagtgg attggaaata ttgatcctta ttatggtggt 600
actacctaca accggaagtt caagggcaag gccacattga ctgtagacaa atcctccagc 660
acagcctaca tgcagctcaa gagtctgaca tctgaggact ctgcagtcta ttactgtgca 720
agatcggtcg gccctatgga ctactggggt caaggaacct cagtcaccgt ctcctcgagc 780
gagcccaaat cttctgacaa aactcacaca tctccaccgt gcccagcacc tgaactcctg 840
ggtggaccgt cagtcttcct cttccccccа aaacccaagg acaccctcat gatctcccgg 900
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc 960
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag 1020
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat 1080
ggcaaggagt acaagtgcaa ggtctccaac aaagccctcc cagccccccat cgagaaaacc 1140
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg 1200
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc 1260
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct 1320
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc 1380

aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac 1440
tacacgcaga agagcctctc cctgtctccg ggtaaatga 1479

<210> 30
<211> 492
<212> PRT
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 30

Met	Glu	Ala	Pro	Ala	Gln	Leu	Leu	Phe	Leu	Leu	Leu	Leu	Trp	Leu	Pro
1				5				10						15	
Asp	Thr	Thr	Gly	Glu	Ile	Val	Leu	Thr	Gln	Ser	Pro	Ala	Thr	Leu	Ser
			20					25					30		
Leu	Ser	Pro	Gly	Glu	Arg	Ala	Thr	Leu	Ser	Cys	Arg	Thr	Ser	Glu	Asn
		35					40					45			
Val	Tyr	Ser	Tyr	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro
	50					55					60				
Arg	Leu	Leu	Ile	Tyr	Phe	Ala	Lys	Thr	Leu	Ala	Glu	Gly	Ile	Pro	Ala
65					70					75					80
Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser
				85					90					95	
Ser	Leu	Glu	Pro	Glu	Asp	Phe	Ala	Val	Tyr	Tyr	Cys	Gln	His	His	Ser
			100					105					110		
Asp	Asn	Pro	Trp	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys	Gly
		115					120					125			
Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ala	Ser	Ala
	130					135					140				
Val	Gln	Leu	Gln	Gln	Ser	Gly	Pro	Glu	Ser	Glu	Lys	Pro	Gly	Ala	Ser
145					150					155					160
Val	Lys	Ile	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Ser	Phe	Thr	Gly	Tyr	Asn
				165					170					175	
Met	Asn	Trp	Val	Lys	Gln	Asn	Asn	Gly	Lys	Ser	Leu	Glu	Trp	Ile	Gly
			180					185					190		
Asn	Ile	Asp	Pro	Tyr	Tyr	Gly	Gly	Thr	Thr	Tyr	Asn	Arg	Lys	Phe	Lys
		195					200					205			
Gly	Lys	Ala	Thr	Leu	Thr	Val	Asp	Lys	Ser	Ser	Ser	Thr	Ala	Tyr	Met
	210					215					220				
Gln	Leu	Lys	Ser	Leu	Thr	Ser	Glu	Asp	Ser	Ala	Val	Tyr	Tyr	Cys	Ala
225					230					235					240
Arg	Ser	Val	Gly	Pro	Met	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Ser	Val	Thr
				245					250					255	
Val	Ser	Ser	Ser	Glu	Pro	Lys	Ser	Ser	Asp	Lys	Thr	His	Thr	Ser	Pro
			260					265					270		
Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe
		275					280					285			
Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val
	290					295					300				
Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe
305					310					315					320

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
325 330 335
Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
340 345 350
Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
355 360 365
Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
370 375 380
Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
385 390 395 400
Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
405 410 415
Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
420 425 430
Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
435 440 445
Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
450 455 460
Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
465 470 475 480
Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
485 490

<210> 31
<211> 1479
<212> DNA
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 31
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt 60
gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccaggcga aagagccacc 120
ctctcctgcc gaacaagtga aaatgtttac agctacttag cctggtacca acagaaacct 180
ggccaggctc ctaggctcct catctatttt gcaaaaacct tagcagaagg aattccagcc 240
aggttcagtg gcagtggatc cgggacagac ttcactctca ccatcagcag cctagagcct 300
gaagattttg cagtttatta ctgtcaacat cattccgata atccgtggac attcggccaa 360
gggaccaagg tggaaatcaa aggtggcggt ggctcgggcg gtggtggatc tggaggaggt 420
ggagctagcg cggtccagct gcagcagtct ggacctgagt cggaaaagcc tggcgcttca 480
gtgaagattt cctgcaaggc ttctggttac tcattcactg gctacaatat gaactgggtg 540
aagcagaata atggaaagag ccttgagtgg attggaaata ttgatcctta ttatggtggt 600
actacctaca accggaagtt caagggcaag gccacattga ctgtagacaa atcctccagc 660
acagcctaca tgcagctcaa gagtctgaca tctgaggact ctgcagtcta ttactgtgca 720
agatcggtcg gccctatgga ctactggggt caaggaacct cagtcaccgt ctcctcgagc 780
gagcccaaat cttctgacaa aactcacaca tgcccaccgt gcccagcacc tgaactcctg 840
ggtggaccgt cagtcttcct cttccccccca aaacccaagg acaccctcat gatctcccgg 900
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc 960
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag 1020
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat 1080
ggcaaggagt acaagtgcaa ggtctccaac aaagccctcc cagccccccat cgagaaaacc 1140
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg 1200
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc 1260

gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct 1320
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc 1380
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac 1440
tacacgcaga agagcctctc cctgtctccg ggtaaatga 1479

<210> 32
<211> 492
<212> PRT
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 32

Met	Glu	Ala	Pro	Ala	Gln	Leu	Leu	Phe	Leu	Leu	Leu	Leu	Trp	Leu	Pro
1				5				10						15	
Asp	Thr	Thr	Gly	Glu	Ile	Val	Leu	Thr	Gln	Ser	Pro	Ala	Thr	Leu	Ser
			20					25					30		
Leu	Ser	Pro	Gly	Glu	Arg	Ala	Thr	Leu	Ser	Cys	Arg	Thr	Ser	Glu	Asn
		35					40					45			
Val	Tyr	Ser	Tyr	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro
	50					55					60				
Arg	Leu	Leu	Ile	Tyr	Phe	Ala	Lys	Thr	Leu	Ala	Glu	Gly	Ile	Pro	Ala
65					70					75					80
Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser
				85					90					95	
Ser	Leu	Glu	Pro	Glu	Asp	Phe	Ala	Val	Tyr	Tyr	Cys	Gln	His	His	Ser
			100					105					110		
Asp	Asn	Pro	Trp	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys	Gly
		115					120					125			
Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ala	Ser	Ala
	130					135					140				
Val	Gln	Leu	Gln	Gln	Ser	Gly	Pro	Glu	Ser	Glu	Lys	Pro	Gly	Ala	Ser
145					150					155					160
Val	Lys	Ile	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Ser	Phe	Thr	Gly	Tyr	Asn
				165					170					175	
Met	Asn	Trp	Val	Lys	Gln	Asn	Asn	Gly	Lys	Ser	Leu	Glu	Trp	Ile	Gly
			180					185					190		
Asn	Ile	Asp	Pro	Tyr	Tyr	Gly	Gly	Thr	Thr	Tyr	Asn	Arg	Lys	Phe	Lys
		195					200					205			
Gly	Lys	Ala	Thr	Leu	Thr	Val	Asp	Lys	Ser	Ser	Ser	Thr	Ala	Tyr	Met
	210					215					220				
Gln	Leu	Lys	Ser	Leu	Thr	Ser	Glu	Asp	Ser	Ala	Val	Tyr	Tyr	Cys	Ala
225					230					235					240
Arg	Ser	Val	Gly	Pro	Met	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Ser	Val	Thr
				245					250					255	
Val	Ser	Ser	Ser	Glu	Pro	Lys	Ser	Ser	Asp	Lys	Thr	His	Thr	Cys	Pro
			260					265					270		
Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe
		275					280					285			
Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val
	290					295					300				

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
305 310 315 320
Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
325 330 335
Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
340 345 350
Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
355 360 365
Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
370 375 380
Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
385 390 395 400
Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
405 410 415
Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
420 425 430
Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
435 440 445
Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
450 455 460
Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
465 470 475 480
Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
485 490

<210> 33
<211> 1479
<212> DNA
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 33
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt 60
gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccaggcga aagagccacc 120
ctctcctgcc gaacaagtga aaatgtttac agctacttag cctggtacca acagaaacct 180
ggccaggctc ctaggctcct catctatttt gcaaaaacct tagcagaagg aattccagcc 240
aggttcagtg gcagtggatc cgggacagac ttcactctca ccatcagcag cctagagcct 300
gaagattttg cagtttatta ctgtcaacat cattccgata atccgtggac attcggccaa 360
gggaccaagg tggaaatcaa aggtggcggt ggctcgggcg gtggtggatc tggaggaggt 420
ggagctagcc aggtgcagct ggtggagtct ggtggaggcg tggtccagcc tgggaggtcc 480
ctgagactct cctgtgcagc ctctggattc accttcagtg gctacaatat gaactgggtc 540
cgccagatgc ccgggaaagg cctggagtgg atgggcaata ttgatcctta ttatggtggt 600
actacctaca accggaagtt caagggccag gtcactatct ccgccgacaa gtccatcagc 660
accgcctacc tgcaatggag cagcctgaag gcctcggaca ccgccatgta ttactgtgca 720
cgctcagtcg gccctatgga ctactggggc cgcggcaccc tggtcactgt ctcctcgagc 780
gagcccaaat cttctgacaa aactcacaca tgcccaccgt gcccagcacc tgaactcctg 840
ggtggaccgt cagtcttcct cttccccccа aaacccaagg acaccctcat gatctcccgg 900
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc 960
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag 1020
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat 1080
ggcaaggagt acaagtgcaa ggtctccaac aaagccctcc cagccccca cgagaaaacc 1140

atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg 1200
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc 1260
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct 1320
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc 1380
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac 1440
tacacgcaga agagcctctc cctgtctccg ggtaaatga 1479

<210> 34
<211> 492
<212> PRT
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 34

Met	Glu	Ala	Pro	Ala	Gln	Leu	Leu	Phe	Leu	Leu	Leu	Leu	Trp	Leu	Pro
1				5				10						15	
Asp	Thr	Thr	Gly	Glu	Ile	Val	Leu	Thr	Gln	Ser	Pro	Ala	Thr	Leu	Ser
			20					25					30		
Leu	Ser	Pro	Gly	Glu	Arg	Ala	Thr	Leu	Ser	Cys	Arg	Thr	Ser	Glu	Asn
		35					40					45			
Val	Tyr	Ser	Tyr	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro
	50					55					60				
Arg	Leu	Leu	Ile	Tyr	Phe	Ala	Lys	Thr	Leu	Ala	Glu	Gly	Ile	Pro	Ala
65					70					75					80
Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser
				85					90					95	
Ser	Leu	Glu	Pro	Glu	Asp	Phe	Ala	Val	Tyr	Tyr	Cys	Gln	His	His	Ser
			100					105					110		
Asp	Asn	Pro	Trp	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys	Gly
		115					120					125			
Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ala	Ser	Gln
	130					135					140				
Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Val	Val	Gln	Pro	Gly	Arg	Ser
145					150					155					160
Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Gly	Tyr	Asn
				165					170					175	
Met	Asn	Trp	Val	Arg	Gln	Met	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Met	Gly
			180					185					190		
Asn	Ile	Asp	Pro	Tyr	Tyr	Gly	Gly	Thr	Thr	Tyr	Asn	Arg	Lys	Phe	Lys
		195					200					205			
Gly	Gln	Val	Thr	Ile	Ser	Ala	Asp	Lys	Ser	Ile	Ser	Thr	Ala	Tyr	Leu
	210					215					220				
Gln	Trp	Ser	Ser	Leu	Lys	Ala	Ser	Asp	Thr	Ala	Met	Tyr	Tyr	Cys	Ala
225					230					235					240
Arg	Ser	Val	Gly	Pro	Met	Asp	Tyr	Trp	Gly	Arg	Gly	Thr	Leu	Val	Thr
				245					250					255	
Val	Ser	Ser	Ser	Glu	Pro	Lys	Ser	Ser	Asp	Lys	Thr	His	Thr	Cys	Pro
			260					265					270		
Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe
		275					280					285			

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
290 295 300
Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
305 310 315 320
Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
325 330 335
Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
340 345 350
Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
355 360 365
Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
370 375 380
Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
385 390 395 400
Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
405 410 415
Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
420 425 430
Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
435 440 445
Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
450 455 460
Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
465 470 475 480
Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
485 490

<210> 35
<211> 1479
<212> DNA
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 35
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt 60
gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccaggcga aagagccacc 120
ctctcctgcc gaacaagtga aaatgtttac agctacttag cctggtacca acagaaacct 180
ggccaggctc ctaggctcct catctatttt gcaaaaacct tagcagaagg aattccagcc 240
aggttcagtg gcagtggatc cgggacagac ttcactctca ccatcagcag cctagagcct 300
gaagattttg cagtttatta ctgtcaacat cattccgata atccgtggac attcggccaa 360
gggaccaagg tggaaatcaa aggtggcggt ggctcgggcg gtggtggatc tggaggaggt 420
ggagctagcc aggtgcagct ggtggagtct ggtggaggcg tggtccagcc tgggaggtcc 480
ctgagactct cctgtgcagc ctctggattc accttcagtg gctacaatat gaactgggtc 540
cgccagatgc ccgggaaagg cctggagtgg atgggcaata ttgatcctta ttatggtggt 600
actacctaca accggaagtt caagggccag gtcactatct ccgccgacaa gtccatcagc 660
accgcctacc tgcaatggag cagcctgaag gcctcggaca ccgccatgta ttactgtgca 720
cgctcagtcg gccctatgga ctactggggc cgcggcaccc tggtcactgt ctcctcgagc 780
gagcccaaat cttctgacaa aactcacaca tgcccaccgt gcccagcacc tgaactcctg 840
ggtggaccgt cagtcttcct cttccccccа aaacccaagg acaccctcat gatctcccgg 900
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc 960
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag 1020

tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat 1080
ggcaaggagt acaagtgcaa ggtctccaac aaagccctcc cagccccat cgagaaaacc 1140
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg 1200
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc 1260
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct 1320
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc 1380
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac 1440
tacacgcaga agagcctctc cctgtctccg ggtaaatga 1479

<210> 36
<211> 492
<212> PRT
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 36
Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1 5 10 15
Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser
20 25 30
Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Thr Ser Glu Asn
35 40 45
Val Tyr Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
50 55 60
Arg Leu Leu Ile Tyr Phe Ala Lys Thr Leu Ala Glu Gly Ile Pro Ala
65 70 75 80
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
85 90 95
Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His His Ser
100 105 110
Asp Asn Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Gly
115 120 125
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ala Ser Gln
130 135 140
Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg Ser
145 150 155 160
Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Gly Tyr Asn
165 170 175
Met Asn Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met Gly
180 185 190
Asn Ile Asp Pro Tyr Tyr Gly Gly Thr Thr Tyr Asn Arg Lys Phe Lys
195 200 205
Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
210 215 220
Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
225 230 235 240
Arg Ser Val Gly Pro Met Asp Tyr Trp Gly Arg Gly Thr Leu Val Thr
245 250 255
Val Ser Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr His Thr Ser Pro
260 265 270

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
275 280 285
Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
290 295 300
Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
305 310 315 320
Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
325 330 335
Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
340 345 350
Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
355 360 365
Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
370 375 380
Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
385 390 395 400
Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
405 410 415
Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
420 425 430
Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
435 440 445
Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
450 455 460
Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
465 470 475 480
Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
485 490

<210> 37
<211> 1476
<212> DNA
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 37
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt 60
gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccaggcga aagagccacc 120
ctctcctgcc gaacaagtga aaatgtttac agctacttag cctggtacca acagaaacct 180
ggccaggctc ctaggctcct catctatttt gcaaaaacct tagcagaagg aattccagcc 240
aggttcagtg gcagtggatc cgggacagac ttcactctca ccatcagcag cctagagcct 300
gaagattttg cagtttatta ctgtcaacat cattccgata atccgtggac attcggccaa 360
gggaccaagg tggaaatcaa aggtggcggt ggctcgggcg gtggtggatc tggaggaggt 420
ggggctagcg aggtgcagct ggtggagtct ggtggaggct tggtccagcc tggagggtcc 480
ctgagactct cctgtgcagc ctctggattc accttcagtg gctacaatat gaactgggtc 540
cgccagatgc ccgggaaagg cctggagtgg atgggcaata ttgatcctta ttatggtggt 600
actacctaca accggaagtt caagggccag gtcactatct ccgccgacaa gtccatcagc 660
accgcctacc tgcaatggag cagcctgaag gcctcggaca ccgccatgta ttactgtgca 720
cgctcagtcg gccctatgga ctactggggc cgcggcaccc tggtcactgt ctcctcgagc 780
gagcccaaat cttctgacaa aactcacaca tctccaccgt gcccagcacc tgaactcctg 840
ggtggaccgt cagtcttcct cttccccccа aaacccaagg acaccctcat gatctcccgg 900

```
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc    960
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag   1020
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat   1080
ggcaaggagt acaagtgcaa ggtctccaac aaagccctcc cagccccat cgagaaaacc    1140
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg   1200
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc   1260
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct   1320
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc   1380
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac   1440
tacacgcaga agagcctctc cctgtctccg ggtaaa                              1476

<210>  38
<211>  492
<212>  PRT
<213>  Artificial sequence

<220>
<223>  CD37 specific binding protein

<400>  38
Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1               5                  10                  15
Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser
            20                  25                  30
Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Thr Ser Glu Asn
        35                  40                  45
Val Tyr Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
    50                  55                  60
Arg Leu Leu Ile Tyr Phe Ala Lys Thr Leu Ala Glu Gly Ile Pro Ala
65                  70                  75                  80
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
                85                  90                  95
Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His His Ser
            100                 105                 110
Asp Asn Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Gly
        115                 120                 125
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ala Ser Glu
    130                 135                 140
Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser
145                 150                 155                 160
Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Gly Tyr Asn
                165                 170                 175
Met Asn Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met Gly
            180                 185                 190
Asn Ile Asp Pro Tyr Tyr Gly Gly Thr Thr Tyr Asn Arg Lys Phe Lys
        195                 200                 205
Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
    210                 215                 220
Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
225                 230                 235                 240
Arg Ser Val Gly Pro Met Asp Tyr Trp Gly Arg Gly Thr Leu Val Thr
                245                 250                 255
```

Val Ser Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr His Thr Ser Pro
260 265 270
Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
275 280 285
Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
290 295 300
Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
305 310 315 320
Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
325 330 335
Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
340 345 350
Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
355 360 365
Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
370 375 380
Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
385 390 395 400
Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
405 410 415
Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
420 425 430
Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
435 440 445
Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
450 455 460
Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
465 470 475 480
Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
485 490

<210> 39
<211> 1476
<212> DNA
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 39
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt 60
gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccaggcga aagagccacc 120
ctctcctgcc gaacaagtga aaatgtttac agctacttag cctggtacca acagaaacct 180
ggccaggctc ctaggctcct catctatttt gcaaaaacct tagcagaagg aattccagcc 240
aggttcagtg gcagtggatc cgggacagac ttcactctca ccatcagcag cctagagcct 300
gaagattttg cagtttatta ctgtcaacat cattccgata atccgtggac attcggccaa 360
gggaccaagg tggaaatcaa aggtggcggt ggctcgggcg gtggtggatc tggaggaggt 420
ggggctagcg aggtgcagct ggtggagtct ggtggaggct tggtccagcc tggagggtcc 480
ctgagactct cctgtgcagc ctctggattc accttcagtg gctacaatat gaactgggtc 540
cgccagatgc ccgggaaagg cctggagtgg atgggcaata ttgatcctta ttatggtggt 600
actacctaca accggaagtt caagggccag gtcactatct ccgccgacaa gtccatcagc 660
accgcctacc tgcaatggag cagcctgaag gcctcggaca ccgccatgta ttactgtgca 720
cgctcagtcg gccctatgga ctactggggc cgcggcaccc tggtcactgt ctcctcgagc 780

gagcccaaat cttctgacaa aactcacaca tgcccaccgt gcccagcacc tgaactcctg 840
ggtggaccgt cagtcttcct cttcccccca aaacccaagg acaccctcat gatctcccgg 900
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc 960
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag 1020
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat 1080
ggcaaggagt acaagtgcaa ggtctccaac aaagccctcc cagccccat cgagaaaacc 1140
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg 1200
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc 1260
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct 1320
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc 1380
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac 1440
tacacgcaga agagcctctc cctgtctccg ggtaaa 1476

<210> 40
<211> 492
<212> PRT
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 40

Met	Glu	Ala	Pro	Ala	Gln	Leu	Leu	Phe	Leu	Leu	Leu	Leu	Trp	Leu	Pro
1				5				10						15	
Asp	Thr	Thr	Gly	Glu	Ile	Val	Leu	Thr	Gln	Ser	Pro	Ala	Thr	Leu	Ser
			20					25					30		
Leu	Ser	Pro	Gly	Glu	Arg	Ala	Thr	Leu	Ser	Cys	Arg	Thr	Ser	Glu	Asn
		35					40					45			
Val	Tyr	Ser	Tyr	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro
	50					55					60				
Arg	Leu	Leu	Ile	Tyr	Phe	Ala	Lys	Thr	Leu	Ala	Glu	Gly	Ile	Pro	Ala
65					70					75					80
Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser
				85					90					95	
Ser	Leu	Glu	Pro	Glu	Asp	Phe	Ala	Val	Tyr	Tyr	Cys	Gln	His	His	Ser
			100					105					110		
Asp	Asn	Pro	Trp	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys	Gly
		115					120					125			
Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ala	Ser	Glu
	130					135					140				
Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly	Ser
145					150					155					160
Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Gly	Tyr	Asn
				165					170					175	
Met	Asn	Trp	Val	Arg	Gln	Met	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Met	Gly
			180					185					190		
Asn	Ile	Asp	Pro	Tyr	Tyr	Gly	Gly	Thr	Thr	Tyr	Asn	Arg	Lys	Phe	Lys
		195					200					205			
Gly	Gln	Val	Thr	Ile	Ser	Ala	Asp	Lys	Ser	Ile	Ser	Thr	Ala	Tyr	Leu
	210					215					220				
Gln	Trp	Ser	Ser	Leu	Lys	Ala	Ser	Asp	Thr	Ala	Met	Tyr	Tyr	Cys	Ala
225					230					235					240

Arg Ser Val Gly Pro Met Asp Tyr Trp Gly Arg Gly Thr Leu Val Thr
245 250 255
Val Ser Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro
260 265 270
Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
275 280 285
Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
290 295 300
Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
305 310 315 320
Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
325 330 335
Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
340 345 350
Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
355 360 365
Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
370 375 380
Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
385 390 395 400
Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
405 410 415
Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
420 425 430
Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
435 440 445
Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
450 455 460
Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
465 470 475 480
Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
485 490

<210> 41
<211> 1476
<212> DNA
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 41
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt 60
gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccaggcga aagagccacc 120
ctctcctgcc gaacaagtga aaatgtttac agctacttag cctggtacca acagaaacct 180
ggccaggctc ctaggctcct catctatttt gcaaaaacct tagcagaagg aattccagcc 240
aggttcagtg gcagtggatc cgggacagac ttcactctca ccatcagcag cctagagcct 300
gaagattttg cagtttatta ctgtcaacat cattccgata atccgtggac attcggccaa 360
gggaccaagg tggaaatcaa aggtggcggt ggctcgggcg gtggtggatc tggaggaggt 420
ggggctagcg aggtgcagct ggtggagtct ggtggaggct ctgtccagcc tggagggtcc 480
ctgagactct cctgtgcagc ctctggattc accttcagtg gctacaatat gaactgggtc 540
cgccagatgc ccgggaaagg cctggagtgg atgggcaata ttgatcctta ttatggtggt 600
actacctaca accggaagtt caagggccag gtcactatct ccgccgacaa gtccatcagc 660

accgcctacc tgcaatggag cagcctgaag gcctcggaca ccgccatgta ttactgtgca 720
cgctcagtcg gccctatgga ctactggggc cgcggcaccc tggtcactgt ctcctcgagc 780
gagcccaaat cttctgacaa aactcacaca tctccaccgt gcccagcacc tgaactcctg 840
ggtggaccgt cagtcttcct cttcccccca aaacccaagg acaccctcat gatctcccgg 900
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc 960
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag 1020
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat 1080
ggcaaggagt acaagtgcaa ggtctccaac aaagccctcc cagccccccat cgagaaaacc 1140
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg 1200
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc 1260
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct 1320
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc 1380
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac 1440
tacacgcaga agagcctctc cctgtctccg ggtaaa 1476

<210> 42
<211> 492
<212> PRT
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 42
Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1 5 10 15
Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser
20 25 30
Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Thr Ser Glu Asn
35 40 45
Val Tyr Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
50 55 60
Arg Leu Leu Ile Tyr Phe Ala Lys Thr Leu Ala Glu Gly Ile Pro Ala
65 70 75 80
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
85 90 95
Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His His Ser
100 105 110
Asp Asn Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Gly
115 120 125
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ala Ser Glu
130 135 140
Val Gln Leu Val Glu Ser Gly Gly Gly Ser Val Gln Pro Gly Gly Ser
145 150 155 160
Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Gly Tyr Asn
165 170 175
Met Asn Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met Gly
180 185 190
Asn Ile Asp Pro Tyr Tyr Gly Gly Thr Thr Tyr Asn Arg Lys Phe Lys
195 200 205
Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
210 215 220

```
Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
225                 230                 235                 240
Arg Ser Val Gly Pro Met Asp Tyr Trp Gly Arg Gly Thr Leu Val Thr
                245                 250                 255
Val Ser Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr His Thr Ser Pro
            260                 265                 270
Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
        275                 280                 285
Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
    290                 295                 300
Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
305                 310                 315                 320
Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
                325                 330                 335
Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
            340                 345                 350
Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
        355                 360                 365
Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
    370                 375                 380
Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
385                 390                 395                 400
Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
                405                 410                 415
Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
            420                 425                 430
Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
        435                 440                 445
Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
    450                 455                 460
Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
465                 470                 475                 480
Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
                485                 490
```

<210> 43
<211> 1476
<212> DNA
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 43

```
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt     60
gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccaggcga aagagccacc    120
ctctcctgcc gaacaagtga aaatgtttac agctacttag cctggtacca acagaaacct    180
ggccaggctc ctaggctcct catctatttt gcaaaaacct tagcagaagg aattccagcc    240
aggttcagtg gcagtggatc cgggacagac ttcactctca ccatcagcag cctagagcct    300
gaagattttg cagtttatta ctgtcaacat cattccgata atccgtggac attcggccaa    360
gggaccaagg tggaaatcaa aggtggcggt ggctcgggcg gtggtggatc tggaggaggt    420
ggggctagcg aggtgcagct ggtggagtct ggtggaggct ctgtccagcc tggagggtcc    480
ctgagactct cctgtgcagc ctctggattc accttcagtg gctacaatat gaactgggtc    540
```

cgccagatgc ccgggaaagg cctggagtgg atgggcaata ttgatcctta ttatggtggt 600
actacctaca accggaagtt caagggccag gtcactatct ccgccgacaa gtccatcagc 660
accgcctacc tgcaatggag cagcctgaag gcctcggaca ccgccatgta ttactgtgca 720
cgctcagtcg gccctatgga ctactggggc cgcggcaccc tggtcactgt ctcctcgagc 780
gagcccaaat cttctgacaa aactcacaca tgcccaccgt gcccagcacc tgaactcctg 840
ggtggaccgt cagtcttcct cttccccccа aaacccaagg acaccctcat gatctcccgg 900
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc 960
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag 1020
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat 1080
ggcaaggagt acaagtgcaa ggtctccaac aaagccctcc cagccccccat cgagaaaacc 1140
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg 1200
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc 1260
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct 1320
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc 1380
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac 1440
tacacgcaga agagcctctc cctgtctccg ggtaaa 1476

<210> 44
<211> 492
<212> PRT
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 44
Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1 5 10 15
Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser
20 25 30
Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Thr Ser Glu Asn
35 40 45
Val Tyr Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
50 55 60
Arg Leu Leu Ile Tyr Phe Ala Lys Thr Leu Ala Glu Gly Ile Pro Ala
65 70 75 80
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
85 90 95
Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His His Ser
100 105 110
Asp Asn Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Gly
115 120 125
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ala Ser Glu
130 135 140
Val Gln Leu Val Glu Ser Gly Gly Gly Ser Val Gln Pro Gly Gly Ser
145 150 155 160
Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Gly Tyr Asn
165 170 175
Met Asn Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met Gly
180 185 190
Asn Ile Asp Pro Tyr Tyr Gly Gly Thr Thr Tyr Asn Arg Lys Phe Lys
195 200 205

```
Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
    210                 215                 220
Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
225                 230                 235                 240
Arg Ser Val Gly Pro Met Asp Tyr Trp Gly Arg Gly Thr Leu Val Thr
                245                 250                 255
Val Ser Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro
            260                 265                 270
Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
        275                 280                 285
Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
    290                 295                 300
Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
305                 310                 315                 320
Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
                325                 330                 335
Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
            340                 345                 350
Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
        355                 360                 365
Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
    370                 375                 380
Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
385                 390                 395                 400
Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
                405                 410                 415
Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
            420                 425                 430
Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
        435                 440                 445
Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
    450                 455                 460
Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
465                 470                 475                 480
Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
                485                 490
```

<210> 45
<211> 1482
<212> DNA
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 45

```
atggaagccc cagctcagct tctcttcctc ctgctactct ggctcccaga taccaccgga     60
gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccaggcga aagagccacc    120
ctctcctgcc gagcaagtca aagtgtttac agctacttag cctggtacca acagaaacct    180
ggccaggctc ctaggctcct catctatttt gcaaaaacct tagcagaagg aattccagcc    240
aggttcagtg gcagtggatc cgggacagac ttcactctca ccatcagcag cctagagcct    300
gaagattttg cagtttatta ctgtcaacat cattccgata atccgtggac attcggccaa    360
gggaccaagg tggaaatcaa aggtggcggt ggctcgggcg gtggtggatc tggaggaggt    420
```

gggaccggtg aggtgcagct ggtgcagtct ggagcagagg tgaaaaagcc cggagagtct 480
ctgaagattt cctgtaaggg atccggttac tcattcactg gctacaatat gaactgggtg 540
cgccagatgc ccgggaaagg cctcgagtgg atgggcaata ttgatcctta ttatggtggt 600
actacctaca accggaagtt caagggccag gtcactatct ccgccgacaa gtccatcagc 660
accgcctacc tgcaatggag cagcctgaag gcctcggaca ccgccatgta ttactgtgca 720
cgctcagtcg gccctatgga ctactggggc cgcggcaccc tggtcactgt ctcctctgat 780
caggagccca aatcttctga caaaactcac acatctccac cgtgcccagc acctgaactc 840
ctgggtggac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc 900
cggacccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag 960
ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag 1020
cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg 1080
aatggcaagg agtacaagtg caaggtctcc aacaaagccc tcccagcccc catcgagaaa 1140
accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gcccccatcc 1200
cgggatgagc tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatcca 1260
agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg 1320
cctcccgtgc tggactccga cggctccttc ttcctctaca gcaagctcac cgtggacaag 1380
agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac 1440
cactacacgc agaagagcct ctccctgtct ccgggtaaat ga 1482

<210> 46
<211> 493
<212> PRT
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 46

Met	Glu	Ala	Pro	Ala	Gln	Leu	Leu	Phe	Leu	Leu	Leu	Leu	Trp	Leu	Pro
1				5				10						15	
Asp	Thr	Thr	Gly	Glu	Ile	Val	Leu	Thr	Gln	Ser	Pro	Ala	Thr	Leu	Ser
			20					25					30		
Leu	Ser	Pro	Gly	Glu	Arg	Ala	Thr	Leu	Ser	Cys	Arg	Ala	Ser	Gln	Ser
		35					40					45			
Val	Tyr	Ser	Tyr	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro
	50					55					60				
Arg	Leu	Leu	Ile	Tyr	Phe	Ala	Lys	Thr	Leu	Ala	Glu	Gly	Ile	Pro	Ala
65					70					75					80
Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser
				85					90					95	
Ser	Leu	Glu	Pro	Glu	Asp	Phe	Ala	Val	Tyr	Tyr	Cys	Gln	His	His	Ser
			100					105					110		
Asp	Asn	Pro	Trp	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys	Gly
		115					120					125			
Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Thr	Gly	Glu
	130					135					140				
Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Glu	Ser
145				150					155					160	
Leu	Lys	Ile	Ser	Cys	Lys	Gly	Ser	Gly	Tyr	Ser	Phe	Thr	Gly	Tyr	Asn
				165					170					175	
Met	Asn	Trp	Val	Arg	Gln	Met	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Met	Gly
			180					185					190		

Asn Ile Asp Pro Tyr Tyr Gly Gly Thr Thr Tyr Asn Arg Lys Phe Lys
195 200 205
Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
210 215 220
Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
225 230 235 240
Arg Ser Val Gly Pro Met Asp Tyr Trp Gly Arg Gly Thr Leu Val Thr
245 250 255
Val Ser Ser Asp Gln Glu Pro Lys Ser Ser Asp Lys Thr His Thr Ser
260 265 270
Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
275 280 285
Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
290 295 300
Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
305 310 315 320
Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
325 330 335
Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
340 345 350
Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
355 360 365
Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
370 375 380
Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
385 390 395 400
Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
405 410 415
Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
420 425 430
Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
435 440 445
Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
450 455 460
Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
465 470 475 480
His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
485 490

<210> 47
<211> 1500
<212> DNA
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 47
aagcttgccg ccatggaagc cccagcgcag cttctcttcc tcctgctact ctggctccca 60
gataccaccg gagaaattgt gttgacacag tctccagcca ccctgtcttt gtctccaggc 120
gaaagagcca ccctctcctg ccgagcaagt gaaaatgttt acagctactt agcctggtac 180
caacagaaac ctggccaggc tcctaggctc ctcatctatt ttgcaaaaac cttagcagaa 240
ggaattccag ccaggttcag tggcagtgga tccgggacag acttcactct caccatcagc 300

agcctagagc ctgaagattt tgcagtttat tactgtcaac atcattccga taatccgtgg 360
acattcggcc aagggaccaa ggtggaaatc aaaggtggcg gcggctcggg cggtggtgga 420
tctggaggag gtgggaccgg tgaggtgcag ctggtgcagt ctggagcaga ggtgaaaaag 480
cccggagagt ctctgaagat ttcctgtaag ggatccggtt actcattcac tggctacaat 540
atgaactggg tgcgccagat gcccgggaaa ggcctcgagt ggatgggcaa tattgatcct 600
tattatggtg gtactaccta caaccggaag ttcaagggcc aggtcactat ctccgccgac 660
aagtccatca gcaccgccta cctgcaatgg agcagcctga aggcctcgga caccgccatg 720
tattactgtg cacgctcagt cggccctttc gactactggg gccagggcac cctggtcact 780
gtctcctctg atcaggagcc caaatcttct gacaaaactc acacatctcc accgtgccca 840
gcacctgaac tcctgggtgg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 900
ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 960
cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 1020
ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 1080
caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc 1140
cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 1200
ctgcccccat cccgggatga gctgaccaag aaccaggtca gcctgacctg cctggtcaaa 1260
ggcttctatc caagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 1320
tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta cagcaagctc 1380
accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 1440
gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtaa atgatctaga 1500

<210> 48
<211> 493
<212> PRT
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 48
Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1 5 10 15
Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser
20 25 30
Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Glu Asn
35 40 45
Val Tyr Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
50 55 60
Arg Leu Leu Ile Tyr Phe Ala Lys Thr Leu Ala Glu Gly Ile Pro Ala
65 70 75 80
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
85 90 95
Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His His Ser
100 105 110
Asp Asn Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Gly
115 120 125
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Thr Gly Glu
130 135 140
Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu Ser
145 150 155 160
Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Gly Tyr Asn
165 170 175

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

<210> 51
<211> 1381
<212> DNA
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 51
aagcttgccg ccatggaagc cccagcgcag cttctcttcc tcctgctact ctggctccca 60
gataccaccg gagaaattgt gttgacacag tctccagcca ccctgtcttt gtctccaggc 120
gaaagagcca ccctctcctg ccgagcaagt gaaaatgttt acagctactt agcctggtac 180

caacagaaac ctggccaggc tcctaggctc ctcatctatt ttgcaaaaac cttagcagaa 240
ggaattccag ccaggttcag tggcagtgga tccgggacag acttcactct caccatcagc 300
agcctagagc ctgaagattt tgcagtttat tactgtcaac atcattccga taatccgtgg 360
acattcggcc aagggaccaa ggtggaaatc aaaggtggcg gtggctcggg cggtggtgga 420
tctggaggag gtgggaccgg tgaggtgcag ctggtgcagt ctggagcaga ggtgaaaaag 480
cccggagagt ctctgaagat ttcctgtaag ggatccggtt actcattcac tggctacaat 540
atgaactggg tgcgccagat gcccgggaaa ggcctcgagt ggatgggcaa tattgatcct 600
tattatggtg gtactaccta caaccggaag ttcaagggcc aggtcactat ctccgccgac 660
aagtccatca gcaccgccta cctgcaatgg agcagcctga aggcctcgga caccgccatg 720
tattactgtg cacgctcagt cggccctttc gactcctggg gccagggcac cctggtcact 780
gtctcctctg atcaggagcc caaatcttct gacaaaactc acacatctcc accgtgccca 840
gcacctgaac tcctgggtgg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 900
ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 960
cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 1020
ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 1080
caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc 1140
cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 1200
ctgcccccat cccgggatga gctgaccaag aaccaggtca gcctgacctg cctggtcaaa 1260
ggcttctatc caagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 1320
tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta cagcaagctc 1380
a 1381

<210> 52
<211> 493
<212> PRT
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 52
Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1 5 10 15
Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser
20 25 30
Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Glu Asn
35 40 45
Val Tyr Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
50 55 60
Arg Leu Leu Ile Tyr Phe Ala Lys Thr Leu Ala Glu Gly Ile Pro Ala
65 70 75 80
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
85 90 95
Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His His Ser
100 105 110
Asp Asn Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Gly
115 120 125
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Thr Gly Glu
130 135 140
Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu Ser
145 150 155 160
Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Gly Tyr Asn
165 170 175

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

<210> 79
<211> 1500
<212> DNA
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 79
aagcttgccg ccatggaagc cccagcgcag cttctcttcc tcctgctact ctggctccca 60
gataccaccg gagaaattgt gttgacacag tctccagcca ccctgtcttt gtctccaggc 120
gaaagagcca ccctctcctg ccgagcaagt gaaaatgttt acagctactt agcctggtac 180

caacagaaac ctggccaggc tcctaggctc ctcatctatt ttgcaaaaac cttagcagaa 240
ggaattccag ccaggttcag tggcagtgga tccgggacag acttcactct caccatcagc 300
agcctagagc ctgaagattt tgcagtttat tactgtcaac atcattccga taatccgtgg 360
acattcggcc aagggaccaa ggtggaaatc aaaggtggcg gtggctcggg cggtggtgga 420
tctggaggag gtgggaccgg tgaggtgcag ctggtgcagt ctggagcaga ggtgaaaaag 480
cccggagagt ctctgaagat ttcctgtaag ggatccggtt actcattcac tggctacaat 540
atgaactggg tgcgccagat gcccgggaaa ggcctcgagt ggatgggcaa tattgatcct 600
tattatggtg gtactaccta caaccggaag ttcaagggcc aggtcactat ctccgccgac 660
aagtccatca gcaccgccta cctgcaatgg agcagcctga aggcctcgga caccgccatg 720
tattactgtg cacgctcagt cggccctttc gacctctggg gcagaggcac cctggtcact 780
gtctcctctg atcaggagcc caaatcttct gacaaaactc acacatctcc accgtgccca 840
gcacctgaac tcctgggtgg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 900
ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 960
cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 1020
ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 1080
caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc 1140
cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 1200
ctgcccccat cccgggatga gctgaccaag aaccaggtca gcctgacctg cctggtcaaa 1260
ggcttctatc caagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 1320
tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta cagcaagctc 1380
accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 1440
gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtaa atgatctaga 1500

<210> 80
<211> 493
<212> PRT
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 80
Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1 5 10 15
Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser
20 25 30
Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Glu Asn
35 40 45
Val Tyr Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
50 55 60
Arg Leu Leu Ile Tyr Phe Ala Lys Thr Leu Ala Glu Gly Ile Pro Ala
65 70 75 80
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
85 90 95
Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His His Ser
100 105 110
Asp Asn Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Gly
115 120 125
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Thr Gly Glu
130 135 140
Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu Ser
145 150 155 160

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

<210> 81
<211> 1494
<212> DNA
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 81
aagcttgccg ccatggaagc cccagctcag cttctcttcc tcctgctact ctggctccca 60
gataccaccg gagaaattgt gttgacacag tctccagcca ccctgtcttt gtctccaggc 120
gaaagagcca ccctctcctg ccgagcaagt gaaaatgttt acagctactt agcctggtac 180
caacagaaac ctggccaggc tcctaggctc ctcatctatt ttgcaaaaac cttagcagaa 240
ggaattccag ccaggttcag tggcagtgga tccgggacag acttcactct caccatcagc 300
agcctagagc ctgaagattt tgcagtttat tactgtcaac atcattccga taatccgtgg 360
acattcggcc aagggaccaa ggtggaaatc aaaggtggcg gtggctcggg cggtggtgga 420
tctggaggag gtggggctag cgaggtgcag ctggtgcagt ctggagcaga ggtgaaaaag 480
cccggagagt ctctgaagat ttcctgtaag ggatccggtt actcattcac tagctacaat 540
atgaactggg tgcgccagat gcccgggaaa ggcctggagt ggatgggcaa tattgatcct 600
tattatggtg gtactaacta cgcccagaag ttccagggcc aggtcactat ctccgccgac 660
aagtccatca gcaccgccta cctgcaatgg agcagcctga aggcctcgga caccgccatg 720
tattactgtg cacgctcagt cggccctatg gactactggg gccgcggcac cctggtcact 780
gtctcctctg atcaggagcc caaatcttct gacaaaactc acacatctcc accgtgccca 840
gcacctgaac tcctgggtgg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 900
ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 960
cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 1020
ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 1080
caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc 1140
cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 1200
ctgccccccat cccgggatga gctgaccaag aaccaggtca gcctgacctg cctggtcaaa 1260
ggcttctatc caagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 1320
tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta cagcaagctc 1380
accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 1440
gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtaa atga 1494

<210> 82
<211> 493
<212> PRT
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 82
Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1 5 10 15
Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser
20 25 30
Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Glu Asn
35 40 45
Val Tyr Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
50 55 60
Arg Leu Leu Ile Tyr Phe Ala Lys Thr Leu Ala Glu Gly Ile Pro Ala
65 70 75 80
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
85 90 95
Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His His Ser
100 105 110
Asp Asn Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Gly
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ala Ser Glu
130 135 140
Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu Ser
145 150 155 160
Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr Asn
165 170 175
Met Asn Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met Gly
180 185 190
Asn Ile Asp Pro Tyr Tyr Gly Gly Thr Asn Tyr Ala Gln Lys Phe Gln
195 200 205
Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
210 215 220
Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
225 230 235 240
Arg Ser Val Gly Pro Met Asp Tyr Trp Gly Arg Gly Thr Leu Val Thr
245 250 255
Val Ser Ser Asp Gln Glu Pro Lys Ser Ser Asp Lys Thr His Thr Ser
260 265 270
Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
275 280 285
Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
290 295 300
Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
305 310 315 320
Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
325 330 335
Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
340 345 350
Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
355 360 365
Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
370 375 380
Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
385 390 395 400
Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
405 410 415
Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
420 425 430
Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
435 440 445
Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
450 455 460
Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
465 470 475 480
His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
485 490

<210> 83
<211> 1476
<212> DNA
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 83
aagcttgccg ccatggaagc cccagcgcag cttctcttcc tcctgctact ctggctccca 60
gataccaccg gagaaattgt gttgacacag tctccagcca ccctgtcttt gtctccaggc 120
gaaagagcca ccctctcctg ccgagcaagt gagaatgttt acagctactt agcctggtac 180
caacagaaac ctggccaggc tcctaggctc ctcatctatt ttgcaaaaac cttagcagaa 240
gggattccag ccagattcag tggcagtggt tccgggacag acttcactct caccatcagc 300
agcctagagc ctgaagattt tgcagtttat tactgtcaac atcattccga taatccgtgg 360
acattcggcc aagggaccaa ggtggaaatc aaaggtggcg gtggctcggg cggtggtgga 420
tctggaggag gtgggagcgg aggaggagct agcgaggtgc agctggtgca gtctggagca 480
gaggtgaaaa agcccggaga gtctctgaag atttcctgta agggatccgg ttactcattc 540
actggctaca atatgaactg ggtgcgccag atgcccggga aaggcctcga atggatgggc 600
aatattgatc cttattatgg tggtactacc tacaaccgga agttcaaggg ccaggtcact 660
atctccgccg acaagtccat cagcaccgcc tacctgcaag gagcagcctg aaggcctcgg 720
acaccgccat gtattactgt gcacgctcag tcggcccttt cgactcctgg ggccagggca 780
ccctggtcac tgtctcgagt tgtccaccgt gcccagcacc tgaactcctg ggtggaccgt 840
cagtcttcct cttccccccа aaacccaagg acaccctcat gatctcccgg acccctgagg 900
tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc aactggtacg 960
tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag tacaacagca 1020
cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat ggcaaggagt 1080
acaagtgcaa ggtctccaac aaagccctcc cagccccat cgagaaaacc atctccaaag 1140
ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg gatgagctga 1200
ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc gacatcgccg 1260
tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct cccgtgctgg 1320
actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc aggtggcagc 1380
aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac tacacgcaga 1440
agagcctctc cctgtctccg ggtaaatgac tctaga 1476

<210> 84
<211> 485
<212> PRT
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 84
Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1 5 10 15
Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser
20 25 30
Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Glu Asn
35 40 45
Val Tyr Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
50 55 60
Arg Leu Leu Ile Tyr Phe Ala Lys Thr Leu Ala Glu Gly Ile Pro Ala
65 70 75 80
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
85 90 95
Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His His Ser
100 105 110

Asp Asn Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Gly
115 120 125
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
130 135 140
Gly Ala Ser Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
145 150 155 160
Pro Gly Glu Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe
165 170 175
Thr Gly Tyr Asn Met Asn Trp Val Arg Gln Met Pro Gly Lys Gly Leu
180 185 190
Glu Trp Met Gly Asn Ile Asp Pro Tyr Tyr Gly Gly Thr Thr Tyr Asn
195 200 205
Arg Lys Phe Lys Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser
210 215 220
Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met
225 230 235 240
Tyr Tyr Cys Ala Arg Ser Val Gly Pro Phe Asp Ser Trp Gly Gln Gly
245 250 255
Thr Leu Val Thr Val Ser Ser Cys Pro Pro Cys Pro Ala Pro Glu Leu
260 265 270
Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
275 280 285
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
290 295 300
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
305 310 315 320
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
325 330 335
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
340 345 350
Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
355 360 365
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
370 375 380
Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
385 390 395 400
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
405 410 415
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
420 425 430
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
435 440 445
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
450 455 460
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
465 470 475 480
Leu Ser Pro Gly Lys
485

<210> 85
<211> 1494
<212> DNA
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 85
aagcttgccg ccatggaagc cccagctcag cttctcttcc tcctgctact ctggctccca 60
gataccaccg gagaaattgt gttgacacag tctccagcca ccctgtcttt gtctccaggc 120
gaaagagcca ccctctcctg ccgaacaagt gaaaatgttt acagctactt agcctggtac 180
caacagaaac ctggccaggc tcctaggctc ctcatctatt ttgcaaaaac cttagcagaa 240
ggaattccag ccaggttcag tggcagtgga tccgggacag acttcactct caccatcagc 300
agcctagagc ctgaagattt tgcagtttat tactgtcaac atcattccga taatccgtgg 360
acattcggcc aagggaccaa ggtggaaatc aaaggtggcg gtggctcggg cggtggtgga 420
tctggaggag gtgggaccgg tgaggtgcag ctggtgcagt ctggagcaga ggtgaaaaag 480
cccggagagt ctctgaagat ttcctgtaag ggatccggtt actcattcac tggctacaat 540
atgaactggg tgcgccagat gcccgggaaa ggcctggagt ggatgggcaa tattgatcct 600
tattatggtg gtactaccta caaccggaag ttcaagggcc aggtcactat ctccgccgac 660
aagtccatca gcaccgccta cctgcaatgg agcagcctga aggcctcgga caccgccatg 720
tattactgtg cacgctcagt cggccctatg gactactggg gccgcggcac cctggtcact 780
gtctcctctg atcaggagcc caaatcttct gacaaaactc acacatctcc accgtgccca 840
gcacctgaac tcctgggtgg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 900
ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 960
cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 1020
ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 1080
caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc 1140
cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 1200
ctgcccccat cccgggatga gctgaccaag aaccaggtca gcctgacctg cctggtcaaa 1260
ggcttctatc caagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 1320
tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta cagcaagctc 1380
accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 1440
gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtaa atga 1494

<210> 86
<211> 493
<212> PRT
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 86
Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1 5 10 15
Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser
20 25 30
Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Thr Ser Glu Asn
35 40 45
Val Tyr Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
50 55 60
Arg Leu Leu Ile Tyr Phe Ala Lys Thr Leu Ala Glu Gly Ile Pro Ala
65 70 75 80
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
85 90 95
Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His His Ser
100 105 110

Asp Asn Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Gly
115 120 125
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ala Ser Glu
130 135 140
Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu Ser
145 150 155 160
Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Gly Tyr Asn
165 170 175
Met Asn Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met Gly
180 185 190
Asn Ile Asp Pro Tyr Tyr Gly Gly Thr Thr Tyr Asn Arg Lys Phe Lys
195 200 205
Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
210 215 220
Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
225 230 235 240
Arg Ser Val Gly Pro Met Asp Tyr Trp Gly Arg Gly Thr Leu Val Thr
245 250 255
Val Ser Ser Asp Gln Glu Pro Lys Ser Ser Asp Lys Thr His Thr Ser
260 265 270
Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
275 280 285
Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
290 295 300
Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
305 310 315 320
Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
325 330 335
Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
340 345 350
Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
355 360 365
Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
370 375 380
Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
385 390 395 400
Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
405 410 415
Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
420 425 430
Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
435 440 445
Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
450 455 460
Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
465 470 475 480
His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
485 490

<210> 87
<211> 1494
<212> DNA
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 87
aagcttgccg ccatggaagc cccagctcag cttctcttcc tcctgctact ctggctccca 60
gataccaccg gtgaaattgt gttgacacag tctccagcca ccctgtcttt gtctccaggc 120
gaaagagcca ccctctcctg ccgaacaagt gaaaatgttt acagctactt agcctggtac 180
caacagaaac ctggccaggc tcctaggctc ctcatctatt ttgcaaaaac cttagcagaa 240
ggaattccag ccaggttcag tggcagtgga tccgggacag acttcactct caccatcagc 300
agcctagagc ctgaagattt tgcagtttat tactgtcaac atcattccga taatccgtgg 360
acattcggcc aagggaccaa ggtggaaatc aaaggtggcg gtggctcggg cggtggtgga 420
tctggaggag gtggggctag cgaggtgcag ctggtgcagt ctggagcaga ggtgaaaaag 480
cccggagagt ctctgaggat ttcctgtaag ggatccggtt actcattcac tggctacaat 540
atgaactggg tgcgccagat gcccgggaaa ggcctggagt ggatgggcaa tattgatcct 600
tattatggtg gtactaccta caaccggaag ttcaagggcc aggtcactat ctccgccgac 660
aagtccatca gcaccgccta cctgcaatgg agcagcctga aggcctcgga caccgccatg 720
tattactgtg cacgctcagt cggccctatg gactactggg gccgcggcac cctggtcact 780
gtctcctctg atcaggagcc caaatcttct gacaaaactc acacatctcc accgtgccca 840
gcacctgaac tcctgggtgg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 900
ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 960
cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 1020
ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 1080
caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc 1140
cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 1200
ctgcccccat cccgggatga gctgaccaag aaccaggtca gcctgacctg cctggtcaaa 1260
ggcttctatc caagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 1320
tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta cagcaagctc 1380
accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 1440
gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtaa atga 1494

<210> 88
<211> 493
<212> PRT
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 88
Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1 5 10 15
Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser
20 25 30
Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Thr Ser Glu Asn
35 40 45
Val Tyr Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
50 55 60
Arg Leu Leu Ile Tyr Phe Ala Lys Thr Leu Ala Glu Gly Ile Pro Ala
65 70 75 80
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
85 90 95
Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His His Ser
100 105 110

Asp Asn Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Gly
115 120 125
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ala Ser Glu
130 135 140
Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu Ser
145 150 155 160
Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Gly Tyr Asn
165 170 175
Met Asn Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met Gly
180 185 190
Asn Ile Asp Pro Tyr Tyr Gly Gly Thr Thr Tyr Asn Arg Lys Phe Lys
195 200 205
Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
210 215 220
Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
225 230 235 240
Arg Ser Val Gly Pro Met Asp Tyr Trp Gly Arg Gly Thr Leu Val Thr
245 250 255
Val Ser Ser Asp Gln Glu Pro Lys Ser Ser Asp Lys Thr His Thr Ser
260 265 270
Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
275 280 285
Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
290 295 300
Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
305 310 315 320
Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
325 330 335
Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
340 345 350
Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
355 360 365
Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
370 375 380
Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
385 390 395 400
Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
405 410 415
Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
420 425 430
Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
435 440 445
Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
450 455 460
Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
465 470 475 480
His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
485 490

<210> 221
<211> 1530
<212> DNA
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 221
aagcttgccg ccatggaagc cccagctcag cttctcttcc tcctgctact ctggctccca 60
gataccaccg gagaggtgca gctggtgcag tctggagcag aggtgaaaaa gcccggagag 120
tctctgaaga tttcctgtaa gggctccggt tactcattca ctggctacaa tatgaactgg 180
gtgcgccaga tgcccgggaa aggcctcgag tggatgggca atattgatcc ttattatggt 240
ggtactacct acaaccggaa gttcaagggc caggtcacta tctccgccga caagtccatc 300
agcaccgcct acctgcaatg gagcagcctg aaggcctcgg acaccgccat gtattactgt 360
gcacgctcag tcggcccttt cgactcctgg ggccagggca ccctggtcac tgtctcctct 420
gggggtggag gctctggtgg cggtggctct ggcggaggtg gatccggtgg cggcggatct 480
ggcgggggtg gctctgaaat tgtgttgaca cagtctccag ccaccctgtc tttgtctcca 540
ggcgaaagag ccaccctctc ctgccgagca agtgaaaatg tttacagcta cttagcctgg 600
taccaacaga aacctggcca ggctcctagg ctcctcatct attttgcaaa aaccttagca 660
gaaggaattc cagccaggtt cagtggcagt ggctccggga cagacttcac tctcaccatc 720
agcagcctag agcctgaaga ttttgcagtt tattactgtc aacatcattc cgataatccg 780
tggacattcg gccaagggac caaggtggaa atcaaaggtg atcaggagcc caaatcttct 840
gacaaaactc acacatctcc accgtgccca gcacctgaac tcctgggtgg accgtcagtc 900
ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca 960
tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca agttcaactg gtacgtggac 1020
ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacaa cagcacgtac 1080
cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag 1140
tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa 1200
gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggatga gctgaccaag 1260
aaccaggtca gcctgacctg cctggtcaaa ggcttctatc caagcgacat cgccgtggag 1320
tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc 1380
gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg 1440
aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 1500
ctctccctgt ctccgggtaa atgatctaga 1530

<210> 222
<211> 503
<212> PRT
<213> Artificial sequence

<220>
<223> CD37 specific binding protein

<400> 222
Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1 5 10 15
Asp Thr Thr Gly Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys
20 25 30
Lys Pro Gly Glu Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser
35 40 45
Phe Thr Gly Tyr Asn Met Asn Trp Val Arg Gln Met Pro Gly Lys Gly
50 55 60
Leu Glu Trp Met Gly Asn Ile Asp Pro Tyr Tyr Gly Gly Thr Thr Tyr
65 70 75 80
Asn Arg Lys Phe Lys Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile
85 90 95

Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala
100 105 110
Met Tyr Tyr Cys Ala Arg Ser Val Gly Pro Phe Asp Ser Trp Gly Gln
115 120 125
Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
130 135 140
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
145 150 155 160
Ser Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro
165 170 175
Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Glu Asn Val Tyr Ser
180 185 190
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
195 200 205
Ile Tyr Phe Ala Lys Thr Leu Ala Glu Gly Ile Pro Ala Arg Phe Ser
210 215 220
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
225 230 235 240
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His His Ser Asp Asn Pro
245 250 255
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Gly Asp Gln Glu
260 265 270
Pro Lys Ser Ser Asp Lys Thr His Thr Ser Pro Pro Cys Pro Ala Pro
275 280 285
Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
290 295 300
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
305 310 315 320
Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
325 330 335
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
340 345 350
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
355 360 365
Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
370 375 380
Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
385 390 395 400
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
405 410 415
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
420 425 430
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
435 440 445
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
450 455 460
Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
465 470 475 480
Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
485 490 495
Leu Ser Leu Ser Pro Gly Lys
500
<210> 254

<211> 473
<212> PRT
<213> Artificial Sequence

<220>
<223> CD37 specific binding protein

<400> 254

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	Glu	Asn	Val	Tyr	Ser	Tyr
			20					25					30		
Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Leu	Leu	Ile
		35					40					45			
Tyr	Phe	Ala	Lys	Thr	Leu	Ala	Glu	Gly	Ile	Pro	Ala	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	Val	Tyr	Tyr	Cys	Gln	His	His	Ser	Asp	Asn	Pro	Trp
			85					90					95		
Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys	Gly	Gly	Gly	Gly	Ser
		100					105					110			
Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Thr	Gly	Glu	Val	Gln	Leu	Val
	115					120					125				
Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Glu	Ser	Leu	Lys	Ile	Ser
130					135					140					
Cys	Lys	Gly	Ser	Gly	Tyr	Ser	Phe	Thr	Gly	Tyr	Asn	Met	Asn	Trp	Val
145				150					155					160	
Arg	Gln	Met	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Met	Gly	Asn	Ile	Asp	Pro
			165					170					175		
Tyr	Tyr	Gly	Gly	Thr	Thr	Tyr	Asn	Arg	Lys	Phe	Lys	Gly	Gln	Val	Thr
		180					185					190			
Ile	Ser	Ala	Asp	Lys	Ser	Ile	Ser	Thr	Ala	Tyr	Leu	Gln	Trp	Ser	Ser
	195					200					205				
Leu	Lys	Ala	Ser	Asp	Thr	Ala	Met	Tyr	Tyr	Cys	Ala	Arg	Ser	Val	Gly
210					215					220					
Pro	Met	Asp	Val	Trp	Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser	Asp
225				230					235					240	
Gln	Glu	Pro	Lys	Ser	Ser	Asp	Lys	Thr	His	Thr	Ser	Pro	Pro	Cys	Pro
			245					250					255		
Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys
		260					265					270			
Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val
	275					280					285				
Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr
290					295					300					
Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu
305				310					315					320	
Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His
			325					330					335		
Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys
		340					345					350			

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
355 360 365
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
370 375 380
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
385 390 395 400
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
405 410 415
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
420 425 430
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
435 440 445
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
450 455 460
Lys Ser Leu Ser Leu Ser Pro Gly Lys
465 470

<210> 262
<211> 493
<212> PRT
<213> Artificial Sequence

<220>
<223> CD37 specific binding protein

<400> 262
Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1 5 10 15
Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser
20 25 30
Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Glu Asn
35 40 45
Val Tyr Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
50 55 60
Arg Leu Leu Ile Tyr Phe Ala Lys Thr Leu Ala Glu Gly Ile Pro Ala
65 70 75 80
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
85 90 95
Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His His Ser
100 105 110
Asp Asn Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Gly
115 120 125
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ala Ser Glu
130 135 140
Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu Ser
145 150 155 160
Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr Asn
165 170 175
Met Asn Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met Gly
180 185 190
Asn Ile Asp Pro Tyr Tyr Gly Gly Thr Gly Tyr Ala Gln Lys Phe Gln
195 200 205

Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
210 215 220
Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
225 230 235 240
Arg Ser Val Gly Pro Met Asp Tyr Trp Gly Arg Gly Thr Leu Val Thr
245 250 255
Val Ser Ser Asp Gln Glu Pro Lys Ser Ser Asp Lys Thr His Thr Ser
260 265 270
Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
275 280 285
Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
290 295 300
Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
305 310 315 320
Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
325 330 335
Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
340 345 350
Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
355 360 365
Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
370 375 380
Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
385 390 395 400
Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
405 410 415
Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
420 425 430
Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
435 440 445
Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
450 455 460
Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
465 470 475 480
His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
485 490

<210> 263
<211> 10
<212> PRT
<213> Homo sapiens

<400> 263
Glu Pro Lys Ser Cys Asp Lys Thr His Thr
1 5 10

<210> 264
<211> 4
<212> PRT
<213> Homo sapiens

<400> 264
Cys Pro Pro Cys
1

<210> 265
<211> 4
<212> PRT
<213> Homo sapiens

<400> 265
Gly Thr Cys Tyr
1

<210> 266
<211> 473
<212> PRT
<213> Artificial Sequence

<220>
<223> CD37 specific binding protein

<400> 266
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 Glu Asn Val Tyr Ser Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Phe Ala Lys Thr Leu Ala Glu Gly Ile Pro Ala 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 Val Tyr Tyr Cys Gln His His Ser Asp Asn Pro Trp
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Gly Gly Gly Gly Ser
100 105 110
Gly Gly Gly Gly Ser Gly Gly Gly Gly Thr Gly Glu Val Gln Leu Val
115 120 125
Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu Ser Leu Lys Ile Ser
130 135 140
Cys Lys Gly Ser Gly Tyr Ser Phe Thr Gly Tyr Asn Met Asn Trp Val
145 150 155 160
Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met Gly Asn Ile Asp Pro
165 170 175
Tyr Tyr Gly Gly Thr Thr Tyr Asn Arg Lys Phe Lys Gly Gln Val Thr
180 185 190
Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu Gln Trp Ser Ser
195 200 205
Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala Arg Ser Val Gly
210 215 220
Pro Phe Asp Pro Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Asp
225 230 235 240

Gln Glu Pro Lys Ser Ser Asp Lys Thr His Thr Ser Pro Pro Cys Pro
245 250 255
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
260 265 270
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
275 280 285
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
290 295 300
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
305 310 315 320
Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
325 330 335
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
340 345 350
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
355 360 365
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
370 375 380
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
385 390 395 400
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
405 410 415
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
420 425 430
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
435 440 445
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
450 455 460
Lys Ser Leu Ser Leu Ser Pro Gly Lys
465 470

<210> 267
<211> 473
<212> PRT
<213> Artificial Sequence

<220>
<223> CD37 specific binding protein

<400> 267
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 Glu Asn Val Tyr Ser Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Phe Ala Lys Thr Leu Ala Glu Gly Ile Pro Ala 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 Val Tyr Tyr Cys Gln His His Ser Asp Asn Pro Trp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Gly Gly Gly Gly Ser
100 105 110
Gly Gly Gly Gly Ser Gly Gly Gly Gly Thr Gly Glu Val Gln Leu Val
115 120 125
Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu Ser Leu Lys Ile Ser
130 135 140
Cys Lys Gly Ser Gly Tyr Ser Phe Thr Gly Tyr Asn Met Asn Trp Val
145 150 155 160
Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met Gly Asn Ile Asp Pro
165 170 175
Tyr Tyr Gly Gly Thr Thr Tyr Asn Arg Lys Phe Lys Gly Gln Val Thr
180 185 190
Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu Gln Trp Ser Ser
195 200 205
Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala Arg Ser Val Gly
210 215 220
Pro Met Glu His Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Asp
225 230 235 240
Gln Glu Pro Lys Ser Ser Asp Lys Thr His Thr Ser Pro Pro Cys Pro
245 250 255
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
260 265 270
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
275 280 285
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
290 295 300
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
305 310 315 320
Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
325 330 335
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
340 345 350
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
355 360 365
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
370 375 380
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
385 390 395 400
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
405 410 415
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
420 425 430
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
435 440 445
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
450 455 460
Lys Ser Leu Ser Leu Ser Pro Gly Lys
465 470

<210> 268
<211> 473
<212> PRT
<213> Artificial Sequence

<220>
<223> CD37 specific binding protein

<400> 268

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	Glu	Asn	Val	Tyr	Ser	Tyr
			20					25					30		
Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Leu	Leu	Ile
		35					40					45			
Tyr	Phe	Ala	Lys	Thr	Leu	Ala	Glu	Gly	Ile	Pro	Ala	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	Val	Tyr	Tyr	Cys	Gln	His	His	Ser	Asp	Asn	Pro	Trp
				85					90					95	
Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys	Gly	Gly	Gly	Gly	Ser
			100					105					110		
Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Thr	Gly	Glu	Val	Gln	Leu	Val
		115					120					125			
Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Glu	Ser	Leu	Lys	Ile	Ser
	130					135					140				
Cys	Lys	Gly	Ser	Gly	Tyr	Ser	Phe	Thr	Gly	Tyr	Asn	Met	Asn	Trp	Val
145					150					155					160
Arg	Gln	Met	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Met	Gly	Asn	Ile	Asp	Pro
				165					170					175	
Tyr	Tyr	Gly	Gly	Thr	Thr	Tyr	Asn	Arg	Lys	Phe	Lys	Gly	Gln	Val	Thr
			180					185					190		
Ile	Ser	Ala	Asp	Lys	Ser	Ile	Ser	Thr	Ala	Tyr	Leu	Gln	Trp	Ser	Ser
		195					200					205			
Leu	Lys	Ala	Ser	Asp	Thr	Ala	Met	Tyr	Tyr	Cys	Ala	Arg	Ser	Val	Gly
	210					215					220				
Pro	Phe	Asp	Val	Trp	Gly	Gln	Gly	Thr	Met	Val	Thr	Val	Ser	Ser	Asp
225					230					235					240
Gln	Glu	Pro	Lys	Ser	Ser	Asp	Lys	Thr	His	Thr	Ser	Pro	Pro	Cys	Pro
				245					250					255	
Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys
			260					265					270		
Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val
		275					280					285			
Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr
	290					295					300				
Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu
305					310					315					320
Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His
				325					330					335	
Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys
			340					345					350		
Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln
		355					360					365			
Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu
	370					375					380				

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
385 390 395 400
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
405 410 415
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
420 425 430
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
435 440 445
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
450 455 460
Lys Ser Leu Ser Leu Ser Pro Gly Lys
465 470

<210> 269
<211> 473
<212> PRT
<213> Artificial Sequence

<220>
<223> CD37 specific binding protein

<400> 269
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 Glu Asn Val Tyr Ser Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Phe Ala Lys Thr Leu Ala Glu Gly Ile Pro Ala 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 Val Tyr Tyr Cys Gln His His Ser Asp Asn Pro Trp
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Gly Gly Gly Gly Ser
100 105 110
Gly Gly Gly Gly Ser Gly Gly Gly Gly Thr Gly Glu Val Gln Leu Val
115 120 125
Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu Ser Leu Lys Ile Ser
130 135 140
Cys Lys Gly Ser Gly Tyr Ser Phe Thr Gly Tyr Asn Met Asn Trp Val
145 150 155 160
Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met Gly Asn Ile Asp Pro
165 170 175
Tyr Tyr Gly Gly Thr Thr Tyr Asn Arg Lys Phe Lys Gly Gln Val Thr
180 185 190
Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu Gln Trp Ser Ser
195 200 205
Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala Arg Ser Val Gly
210 215 220
Pro Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Asp
225 230 235 240

Gln Glu Pro Lys Ser Ser Asp Lys Thr His Thr Ser Pro Pro Cys Pro
245 250 255
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
260 265 270
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
275 280 285
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
290 295 300
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
305 310 315 320
Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
325 330 335
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
340 345 350
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
355 360 365
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
370 375 380
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
385 390 395 400
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
405 410 415
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
420 425 430
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
435 440 445
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
450 455 460
Lys Ser Leu Ser Leu Ser Pro Gly Lys
465 470

CLAIMS

1. A humanized CD37-specific binding molecule, comprising from amino terminus to carboxyl terminus:

(i) a humanized heavy chain variable region,

(ii) a linker as set forth in SEQ ID NO:229,

(iii) a humanized light chain variable region,

(iv) an IgG1 hinge,

(v) human IgG1 CH2 region, and

(vi) human IgG1 CH3 region,

wherein

(a) the humanized heavy chain variable region comprises from amino terminus to carboxyl terminus: a human heavy chain FR1, a heavy chain CDR1 as set forth in SEQ ID NO:63, a human heavy chain FR2, a heavy chain CDR2 as set forth in SEQ ID NO:65, a human heavy chain FR3, a heavy chain CDR3 as set forth in SEQ ID NO:67, 68 or 69, and a human heavy chain FR4, and

(b) the humanized light chain variable region comprises from amino terminus to carboxyl terminus: a human light chain FR1, a light chain CDR1 as set forth in SEQ ID NO:61 or 62, a human light chain FR2, a light chain CDR2 as set forth in SEQ ID NO:64, a human light chain FR3, and a light chain CDR3 as set forth in SEQ ID NO:66, and a human light chain FR4.

2. The humanized CD37-specific binding molecule of claim 1, wherein the human heavy chain FR1 comprises SEQ ID NO:144, the human heavy chain FR2 comprises SEQ ID NO:151, the heavy chain FR3 comprises SEQ ID NO:158, and the heavy chain FR4 comprises SEQ ID NO:161 or 162.

3. The humanized CD37-specific binding molecule of claim 1 or 2, wherein the human light chain FR1 comprises SEQ ID NO:171, the light chain FR2 comprises SEQ ID NO:182, the light chain FR3 comprises SEQ ID NO:195, and the light chain FR4 comprises SEQ ID NO:206.

4. A CD37-specific binding molecule, comprising an amino acid sequence as set forth in SEQ ID NO:253.

5. The CD37-specific binding molecule of claim 4, consisting of the amino acid sequence set forth in SEQ ID NO:253.

6. An isolated nucleic acid molecule, comprising a nucleotide sequence encoding a CD37-specific binding molecule according to any one of claims 1 to 5.

7. A vector comprising a nucleic acid molecule according to claim 6.

8. A host cell comprising a vector according to claim 7.

9. A composition comprising a CD37-specific binding molecule according to any one of claims 1 to 5 and a pharmaceutically acceptable carrier.

10. Use of a CD37-specific binding molecule according to any one of claims 1 to 5, in preparation of a medicament for reducing B-cells.

11. Use of a CD37-specific binding molecule according to any one of claims 1 to 5, for reducing B-cells.

12. Use of a CD37-specific binding molecule according to any one of claims 1 to 5, in preparation of a medicament for treating a disease associated with aberrant B-cell activity.

13. Use of a CD37-specific binding molecule according to any one of claims 1 to 5, for treating a disease associated with aberrant B-cell activity.

14. The use according to claim 12 or 13, wherein the disease associated with aberrant B-cell activity is a B-cell lymphoma, a B-cell leukemia, a B-cell myeloma, a disease characterized by autoantibody production or a disease characterized by inappropriate T-cell stimulation associated with a B-cell pathway.

15. The use according to claim 14, wherein the disease characterized by autoantibody production is idiopathic inflammatory myopathy, rheumatoid arthritis, myasthenia gravis, Grave's disease, type I diabetes mellitus, multiple sclerosis, an autoimmune disease, dermatomyositis, polymyositis or Waldenstrom's macroglobinemia.

16. The use according to claim 12 or 13, wherein the disease associated with aberrant B-cell activity is chronic lymphocytic leukemia (CLL).

17. A composition comprising a CD37-specific binding molecule according to any one of claims 1 to 5 and bendamustine.

18. Use of a CD37-specific binding molecule according to any one of claims 1 to 5 and bendamustine in preparation of a medicament or a combination of medicaments for reducing B-cells.

19. Use of a CD37-specific binding molecule according to any one of claims 1 to 5 and bendamustine in preparation of a medicament or a combination of medicaments for treating a disease associated with aberrant B-cell activity.

20. The use according to claim 19, wherein the disease associated with aberrant B-cell activity is a B-cell lymphoma, a B-cell leukemia, a B-cell myeloma, a disease characterized by autoantibody production or a disease characterized by inappropriate T-cell stimulation associated with a B-cell pathway.

21. The use according to claim 20, wherein the disease characterized by autoantibody production is idiopathic inflammatory myopathy, rheumatoid arthritis, myasthenia gravis, Grave's disease, type I diabetes mellitus, multiple sclerosis, an autoimmune disease, dermatomyositis, polymyositis or Waldenstrom's macroglobinemia.

22. The use according to claim 19, wherein the disease associated with aberrant B-cell activity is chronic lymphocytic leukemia (CLL).

23. The use according to any one of claims 18 to 22, wherein the CD37-specific binding molecule and bendamustine are for concurrent administration.

24. The use according to any one of claims 18 to 22, wherein the CD37-specific binding molecule and bendamustine are for sequential administration.

25. The use according to any one of claims 18 to 22, wherein the CD37-specific binding molecule and bendamustine are for administration in a single formulation.

26. The use according to any one of claims 18 to 25, wherein the CD37-specific binding molecule is a CD37-specific antibody or a small modular immunopharmaceutical molecule.

27. The use according to any one of claims 18 to 25, wherein the CD37-specific binding molecule is a humanized antibody or a humanized small modular immunopharmaceutical molecule.

HEAVY CHAIN

	FR1	CDR1	FR2	CDR2
G28-1	AVQLQQSGPESEKPGASVKISCKASGYSFT	GYNMN	WVKQNNGKSLEWIG	NIDPYYGGTTYNRKFKG
CAS-024	EVQLVQSGAEVKKPGESLKISCKGSGYSFT	GYNMN	WVRQMPGKGLEWMG	NIDPYYGGTTYNRKFKG
Consensus	-VQL-QSG-E--KPG-S-KISCK-SGYSFT	GYNMN	WV-Q--GK-LEW-G	NIDPYYGGTTYNRKFKG

	FR3	CDR3	FR4
G28-1	KATLTVDKSSSTAYMQLKSLTSEDSAVYYCAR	SVGPMDY	WGQGTSVTVSS
CAS-024	QVTISADKSISTAYLQWSSLKASDTAMYYCAR	SVGPFDS	WGQGTLVTVSS
Consensus	--T---DKS-STAY-Q--SL---D-A-YYCAR	SVGP-D-	WGQGT-VTVSS

LIGHT CHAIN

	FR1	CDR1	FR2	CDR2
G28-1	DIQMTQSPASLSASVGETVTITC	RTSENVYSYLA	WYQQKQGKSPQLLVS	FAKTLAE
CAS-024	EIVLTQSPATLSLSPGERATLSC	RASENVYSYLA	WYQQKPGQAPRLLIY	FAKTLAE
Consensus	-I--TQSPATLS-S-GE--T--C	R-SENVYSYLA	WYQQK-G--P-LL--	FAKTLAE

	FR3	CDR3	FR4
G28-1	GVPSRFSGSGSGTQFSLKISSLQPEDSGSYFC	QHHSDNPWT	FGGGTELEIK
CAS-024	GIPARFSGSGSGTDFTLTISSLEPEDFAVYYC	QHHSDNPWT	FGQGTKVEIK
Consensus	G-P-RFSGSGSGT-F-L-ISSL-PED---Y-C	QHHSDNPWT	FG-GT--EIK

Fig. 1

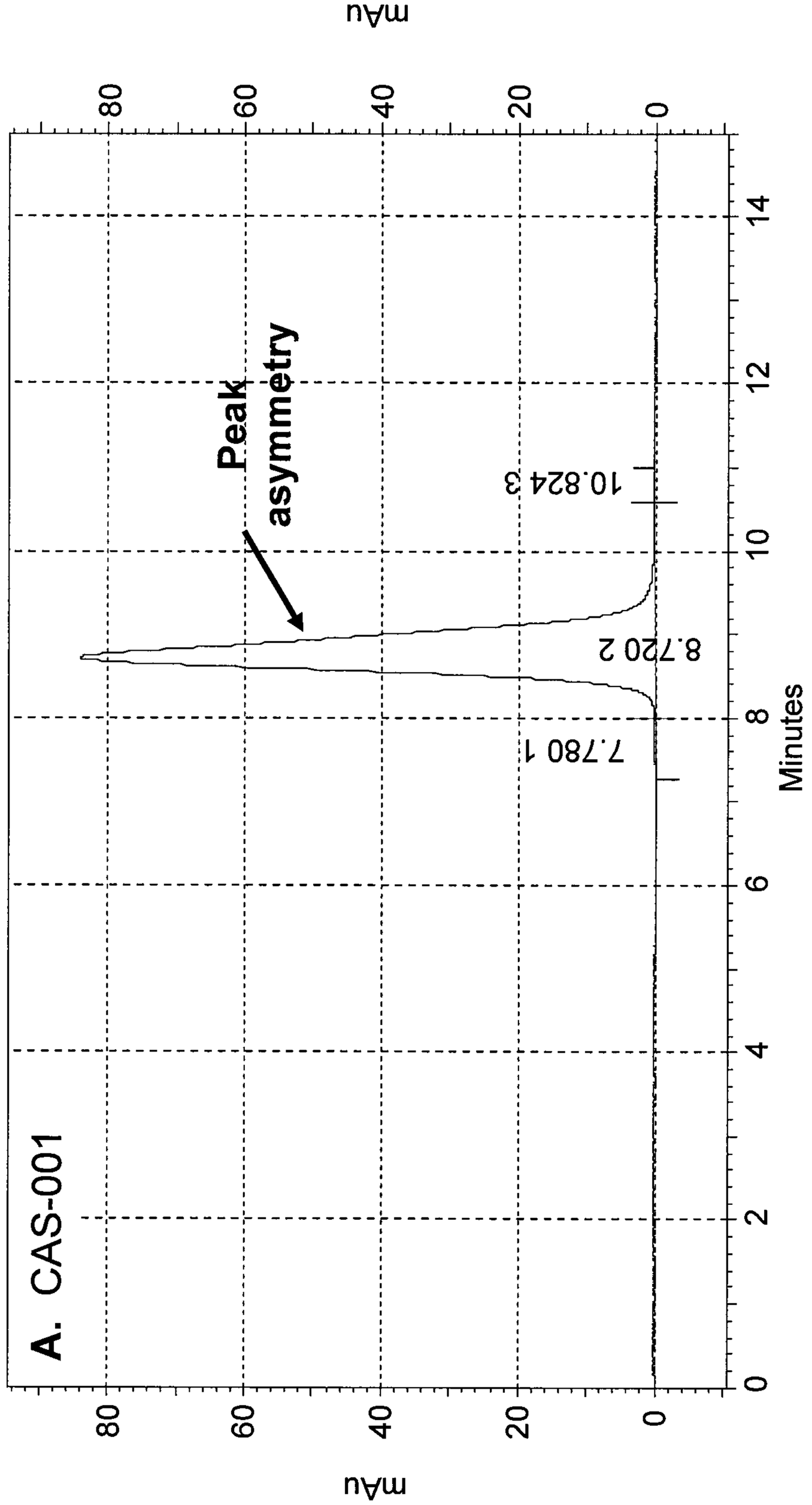
mAu
80
60
40
20
0
14
12
10
8
6
4
2
0
Minutes
Peak asymmetry
10.824 3
8.720 2
7.780 1
A. CAS-001
mAu

Fig. 2A

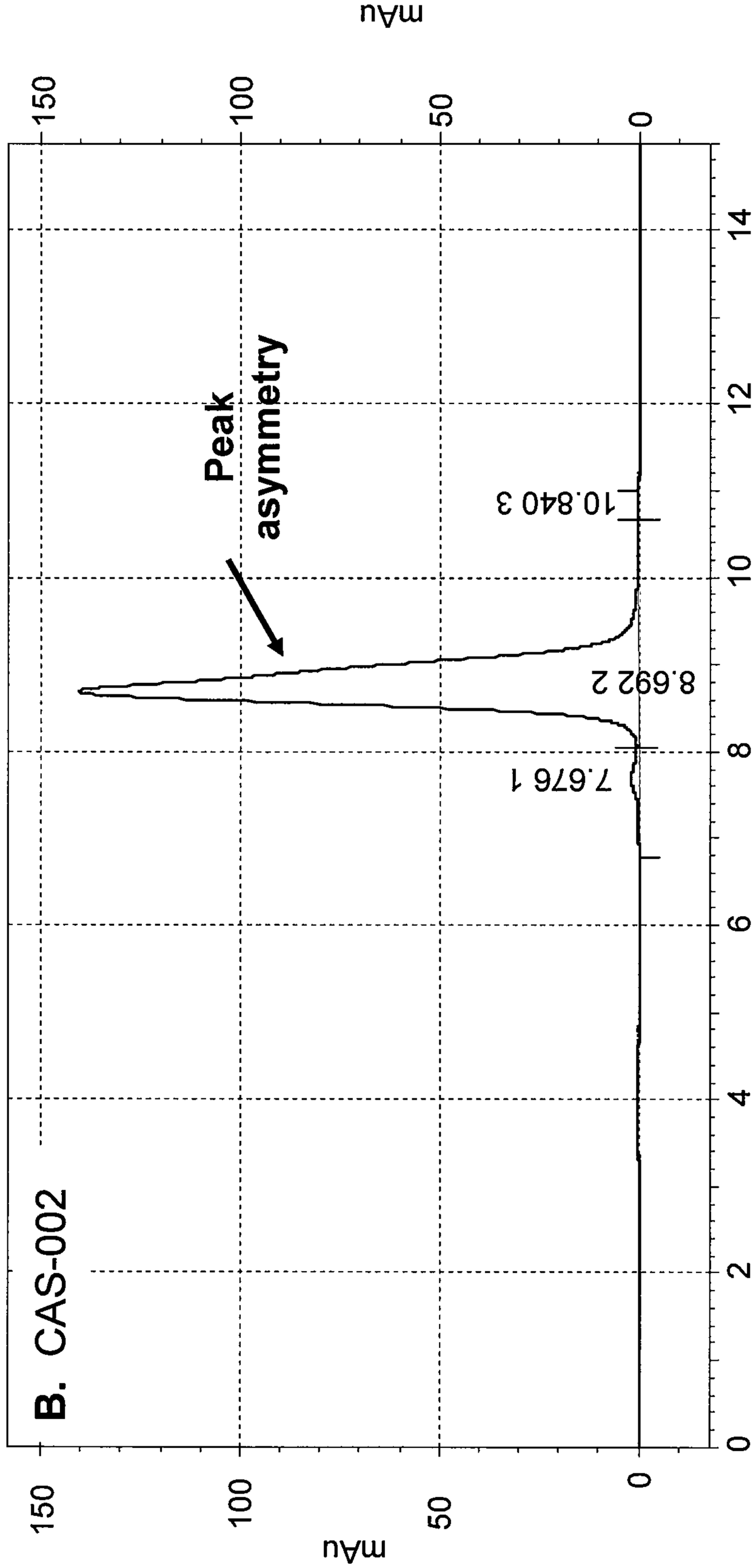
mAu
150
100
50
0
Peak asymmetry
10.840 3
8.692 2
7.676 1
8
10
12
14
Minutes
B. CAS-002
0
2
4
6
mAu

Fig. 2B

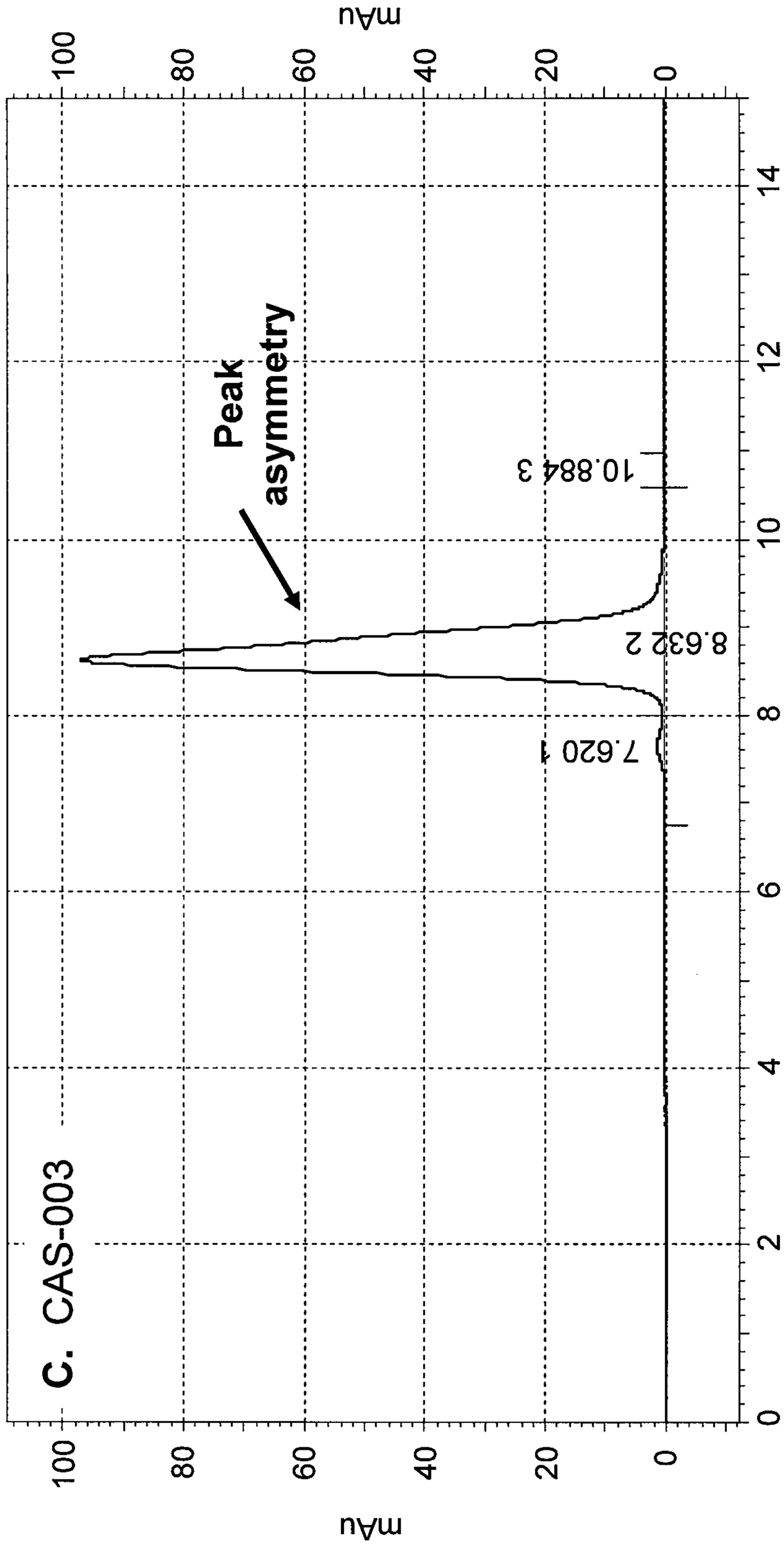
mAu
100
80
60
40
20
0
Peak asymmetry
10.884 3
8.632 2
7.620 1
Minutes
14
12
10
8
6
4
2
0
C. CAS-003
100
80
60
40
20
0
mAu

Fig. 2C

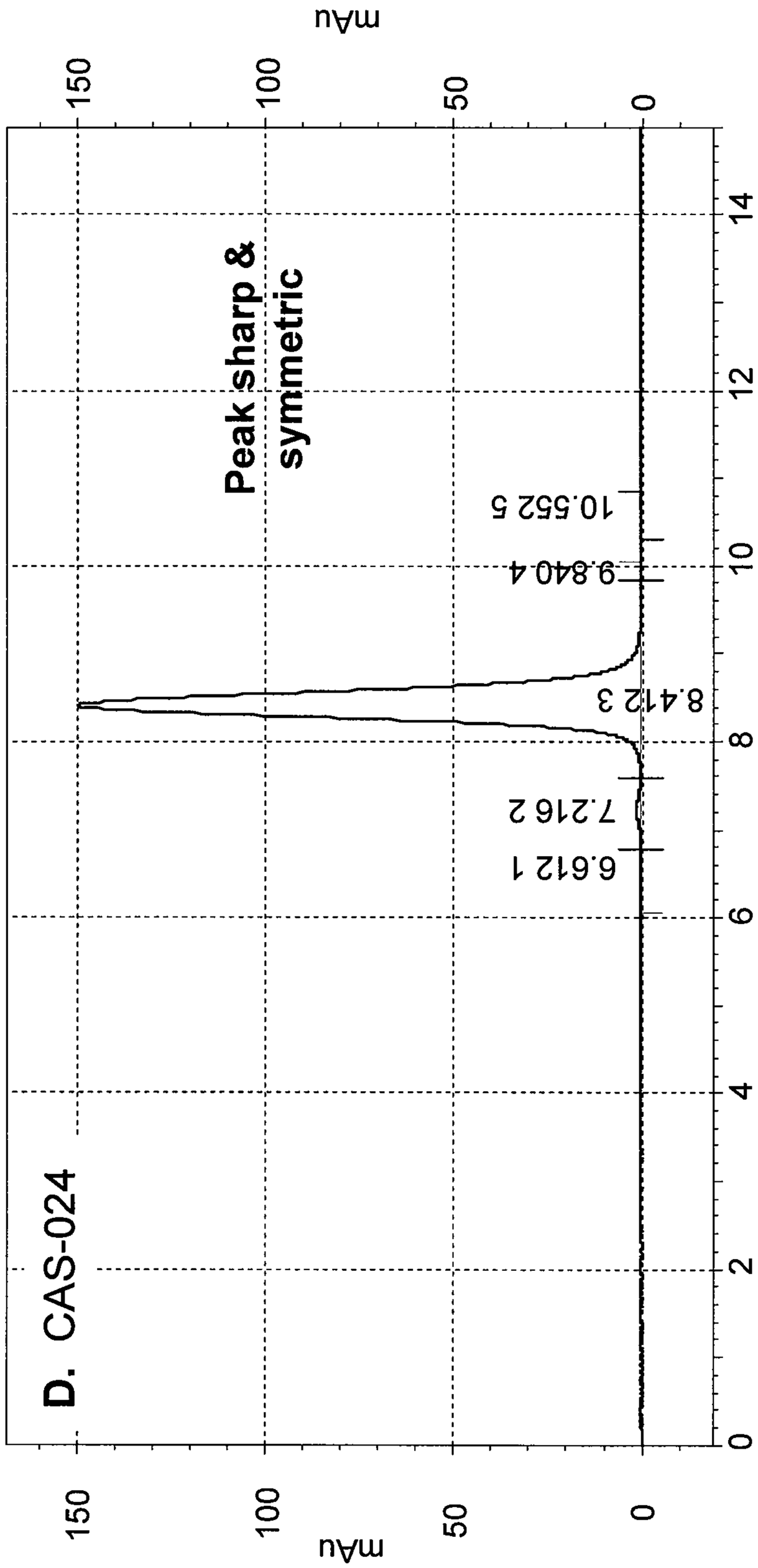
mAu
150
100
50
0
Peak sharp & symmetric
10.552 5
9.840 4
8.412 3
7.216 2
6.612 1
14
12
10
8
6
4
2
0
Minutes
D. CAS-024

Fig. 2D

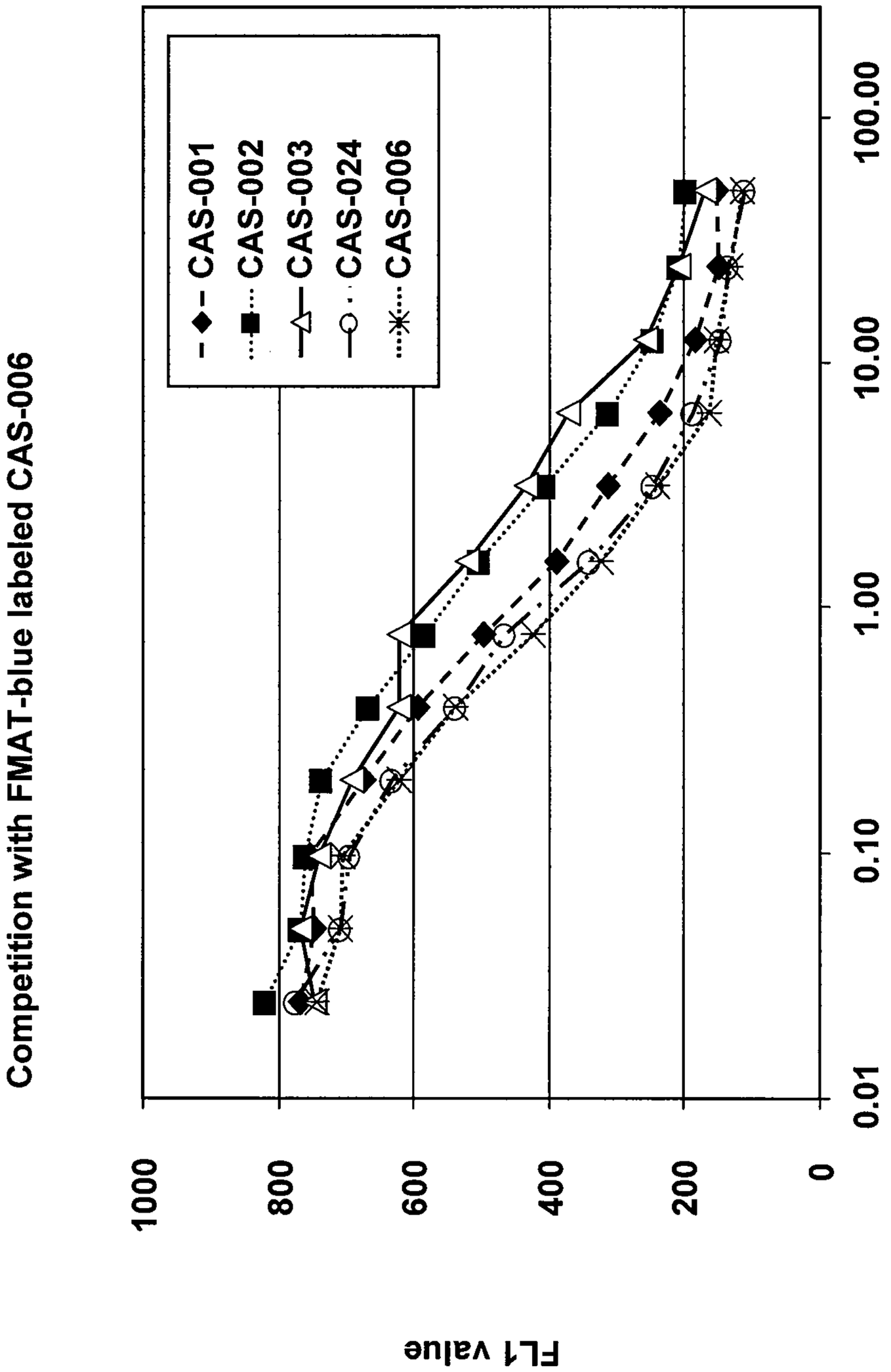
Competition with FMAT-blue labeled CAS-006
FL1 value
1000
800
600
400
200
0
0.01
0.10
1.00
10.00
100.00
µg/ml
CAS-001
CAS-002
CAS-003
CAS-024
CAS-006

Fig. 3

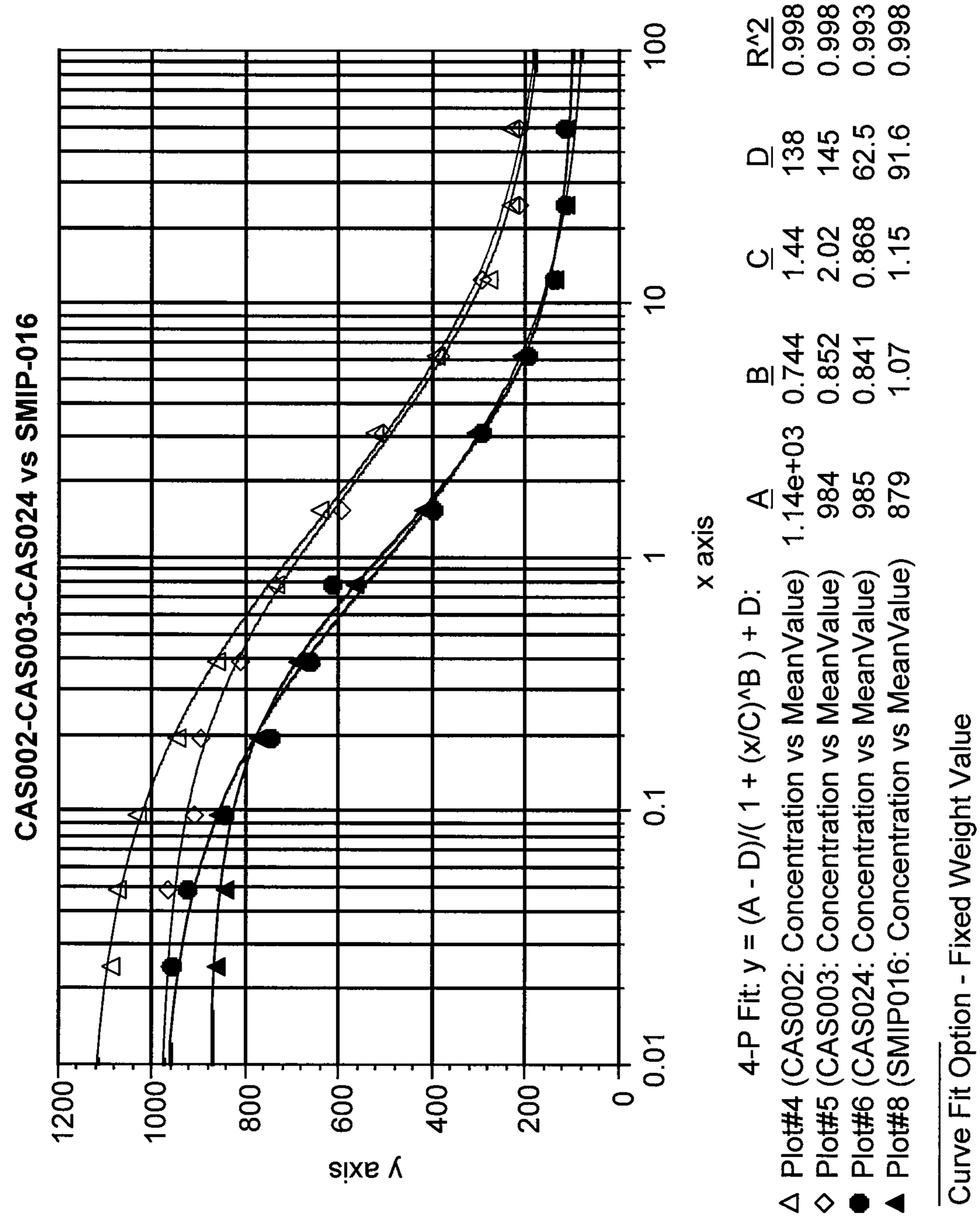
CAS002-CAS003-CAS024 vs SMIP-016
y axis
x axis
1200
1000
800
600
400
200
0
100
10
1
0.1
0.01
4-P Fit: y = (A - D)/(1 + (x/C)^B) + D:
A B C D R^2
1.14e+03 0.744 1.44 138 0.998
984 0.852 2.02 145 0.998
985 0.841 0.868 62.5 0.993
879 1.07 1.15 91.6 0.998
△ Plot#4 (CAS002: Concentration vs MeanValue) 1
◇ Plot#5 (CAS003: Concentration vs MeanValue)
● Plot#6 (CAS024: Concentration vs MeanValue)
◀ Plot#8 (SMIP016: Concentration vs MeanValue)
Curve Fit Option - Fixed Weight Value

Fig. 4A

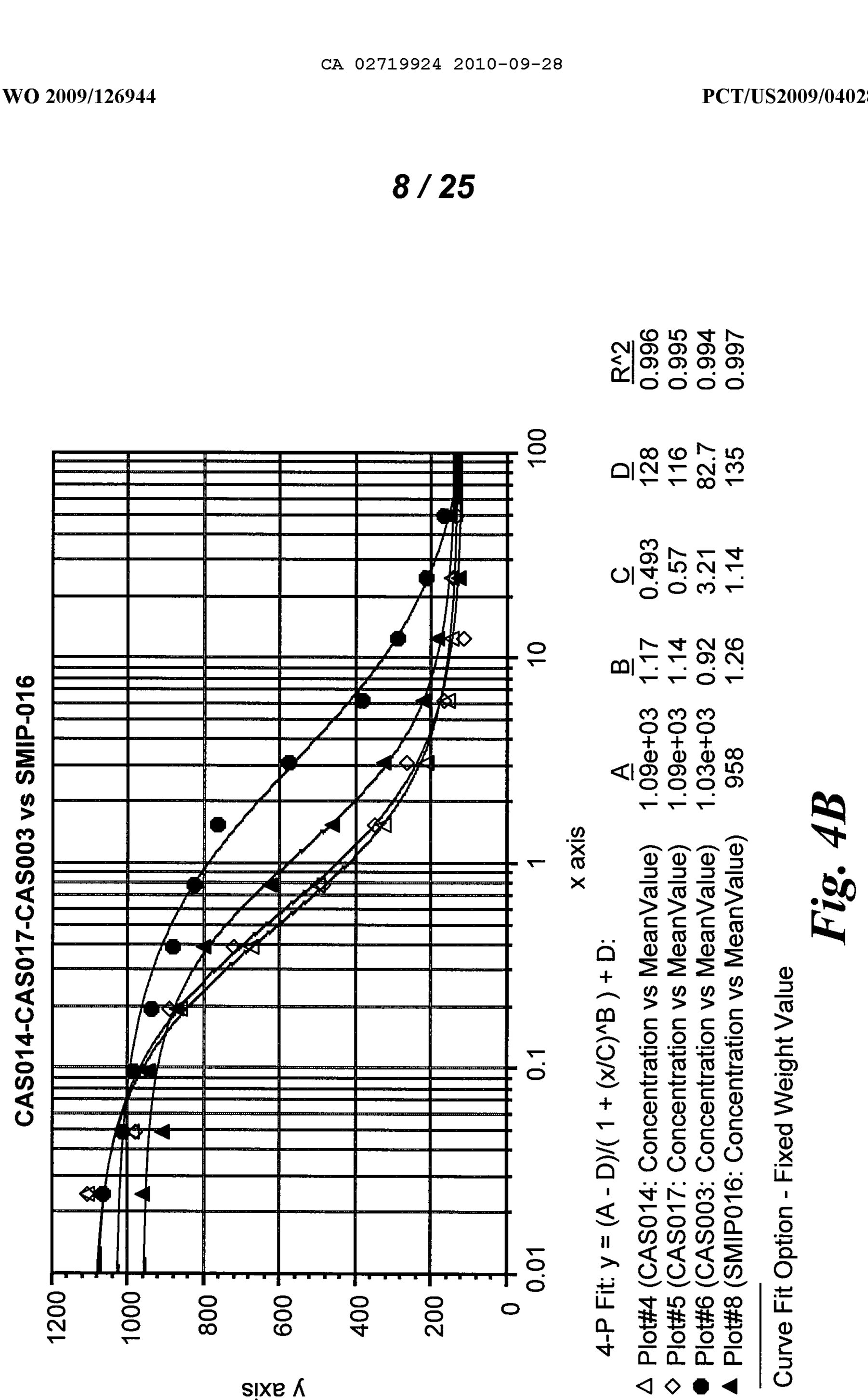
CAS014-CAS017-CAS003 vs SMIP-016
y axis
x axis
1200
1000
800
600
400
200
0
0.01
0.1
1
10
10
R^2
0.996
0.995
0.994
0.997
A B C D
1.09e+03 1.17 0.493 128
1.09e+03 1.14 0.57 116
1.03e+03 0.92 3.21 82.7
958 1.26 1.14 135
4-P Fit: y = (A - D)/(1 + (x/C)^B) + D:
Plot#4 (CAS014: Concentration vs MeanValue)
Plot#5 (CAS017: Concentration vs MeanValue)
Plot#6 (CAS003: Concentration vs MeanValue)
Plot#8 (SMIP016: Concentration vs MeanValue)
Curve Fit Option - Fixed Weight Value

Fig. 4B

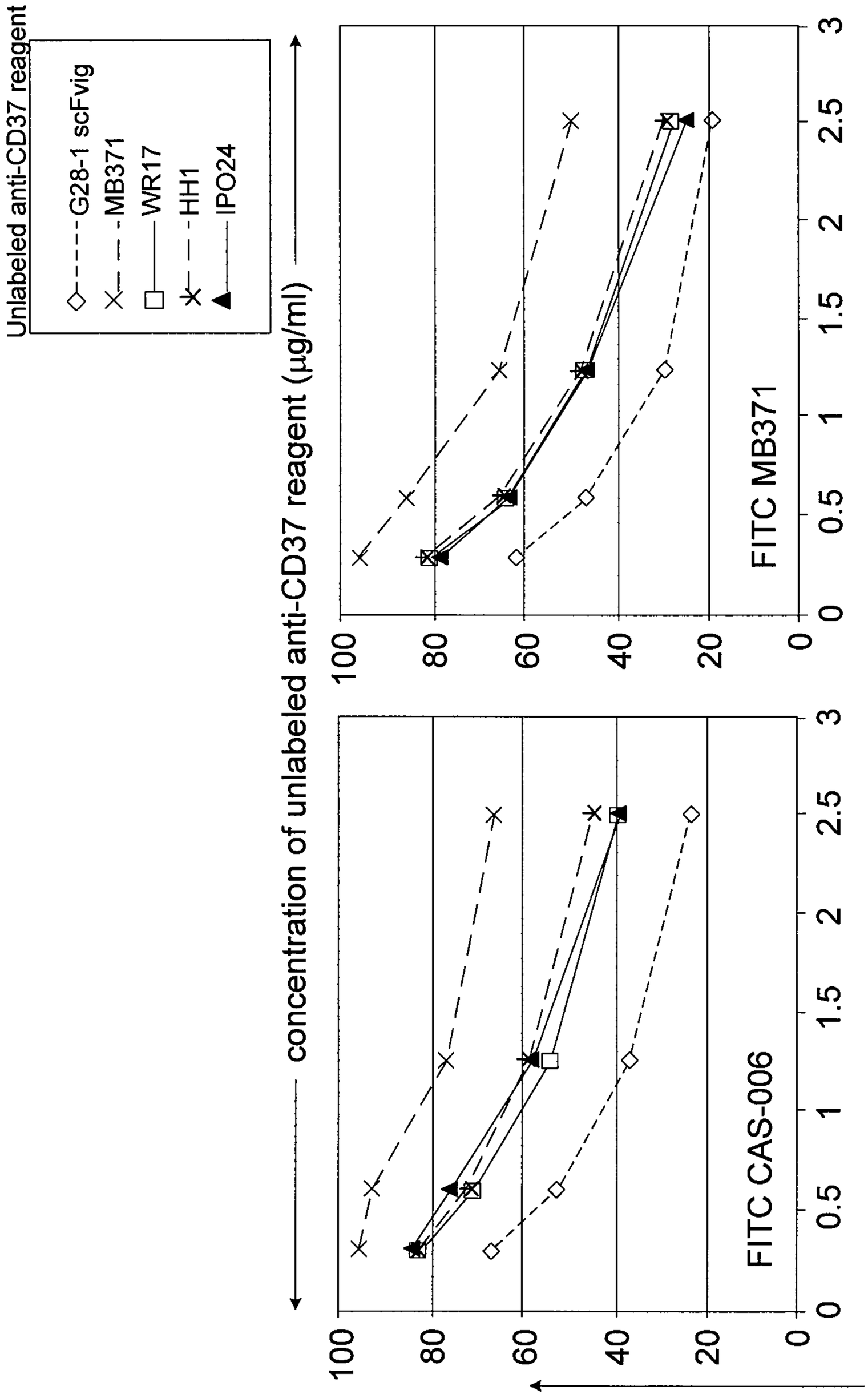
Unlabeled anti-CD37 reagent
G28-1 scFvig
MB371
WR17
HH1
IPO24
concentration of unlabeled anti-CD37 reagent (µg/ml)
FITC MB371
0
0.5
1
1.5
2
2.5
3
100
80
60
40
20
0

Fig. 5B

concentration of unlabeled anti-CD37 reagent (µg/ml)
FITC CAS-006
0
0.5
1
1.5
2
2.5
3
100
80
60
40
20
0

Fig. 5A

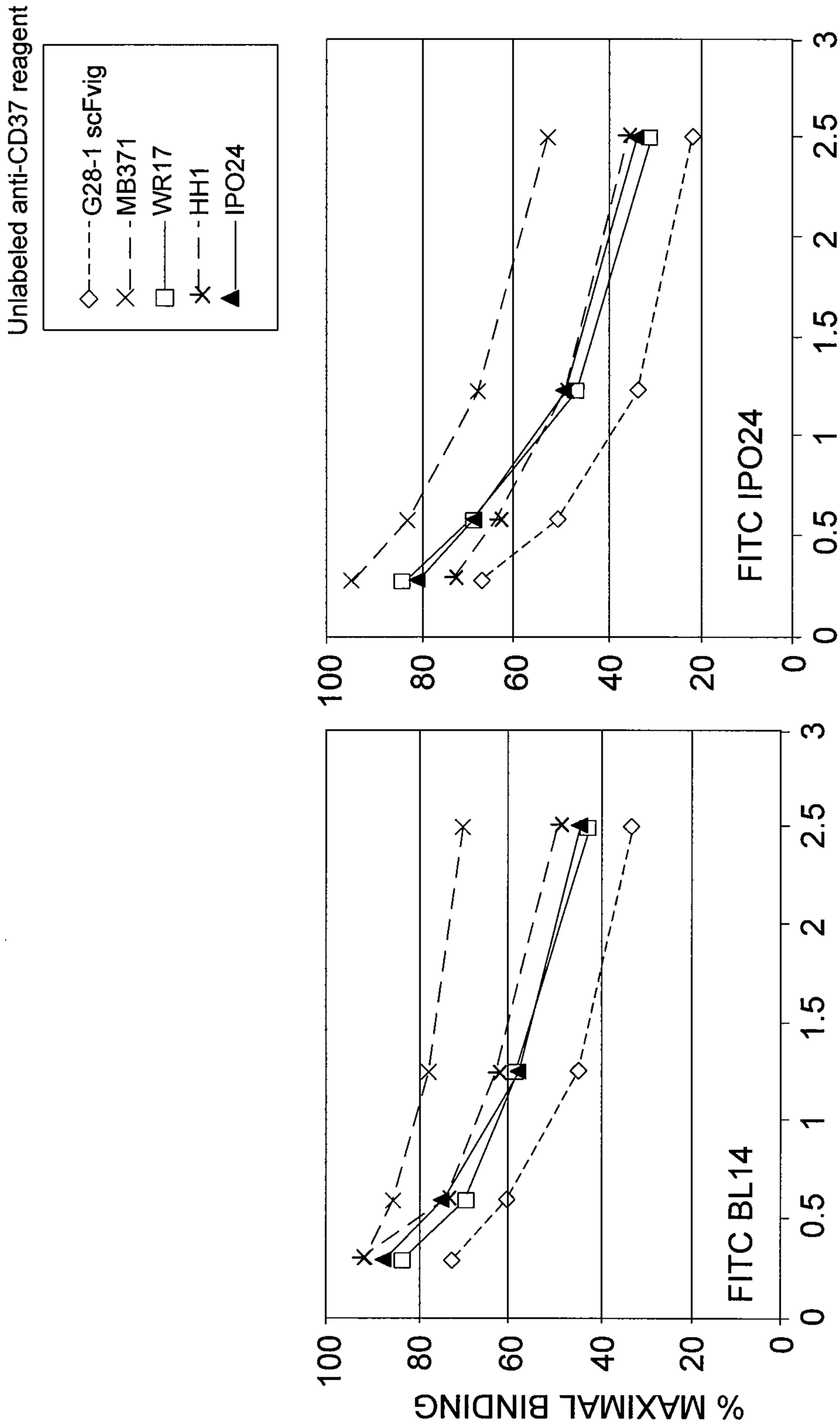
Unlabeled anti-CD37 reagent
G28-1 scFvig
MB371
WR17
HH1
IPO24
FITC IPO24
FITC BL14
% MAXIMAL BINDING
0
20
40
60
80
100
0
0.5
1
1.5
2
2.5
3

Fig. 5D

Fig. 5C

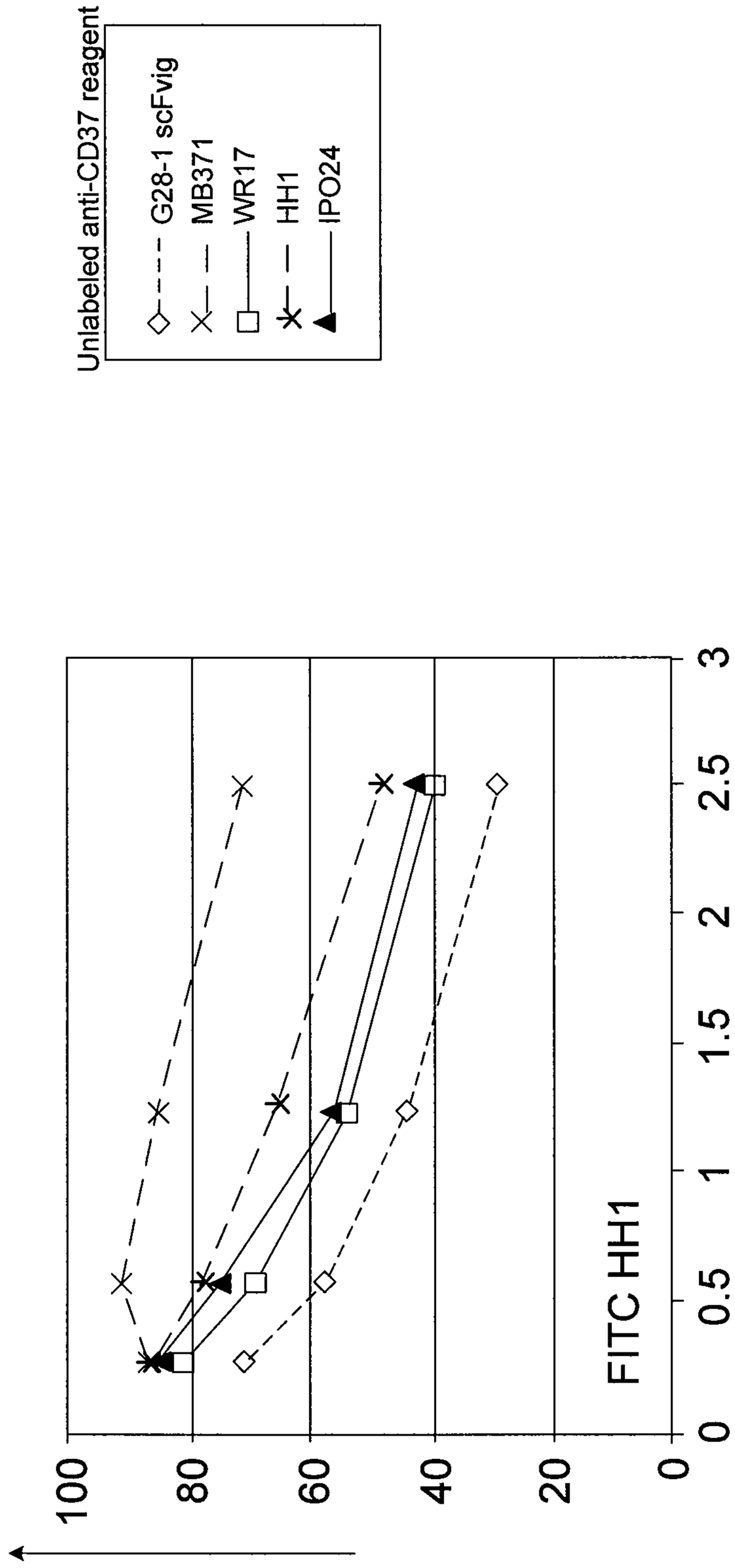
Unlabeled anti-CD37 reagent
G28-1 scFvig
MB371
WR17
HH1
IPO24
FITC HH1
0
0.5
1
1.5
2
2.5
3
100
80
60
40
20
0

Fig. 5E

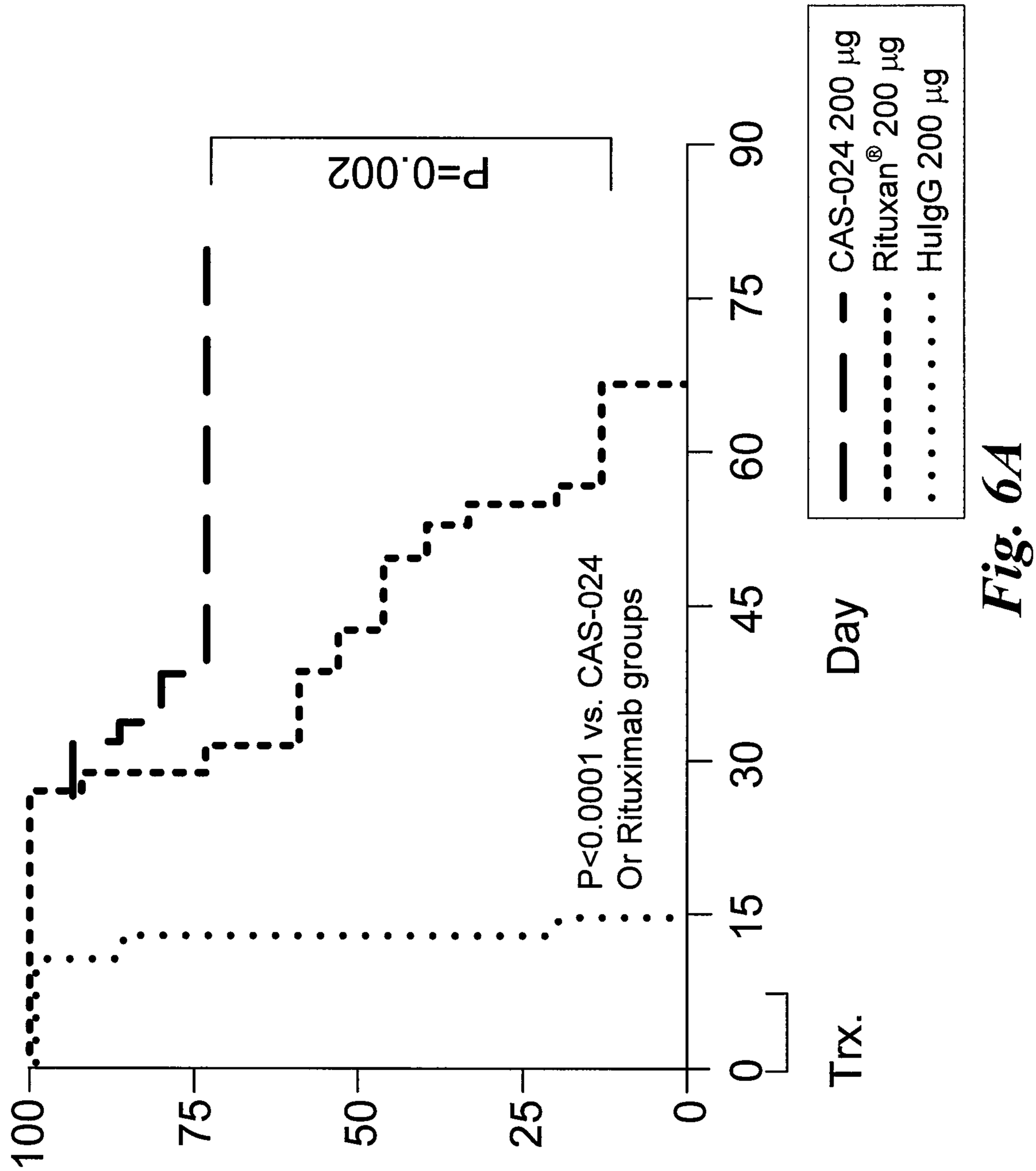
P=0.002
CAS-024 200 µg
Rituxan® 200 µg
HulgG 200 µg
P<0.0001 vs. CAS-024
Or Rituximab groups
% Survival
100
75
50
25
0
Trx.
0
15
30
45
60
75
90
Day

Fig. 6A

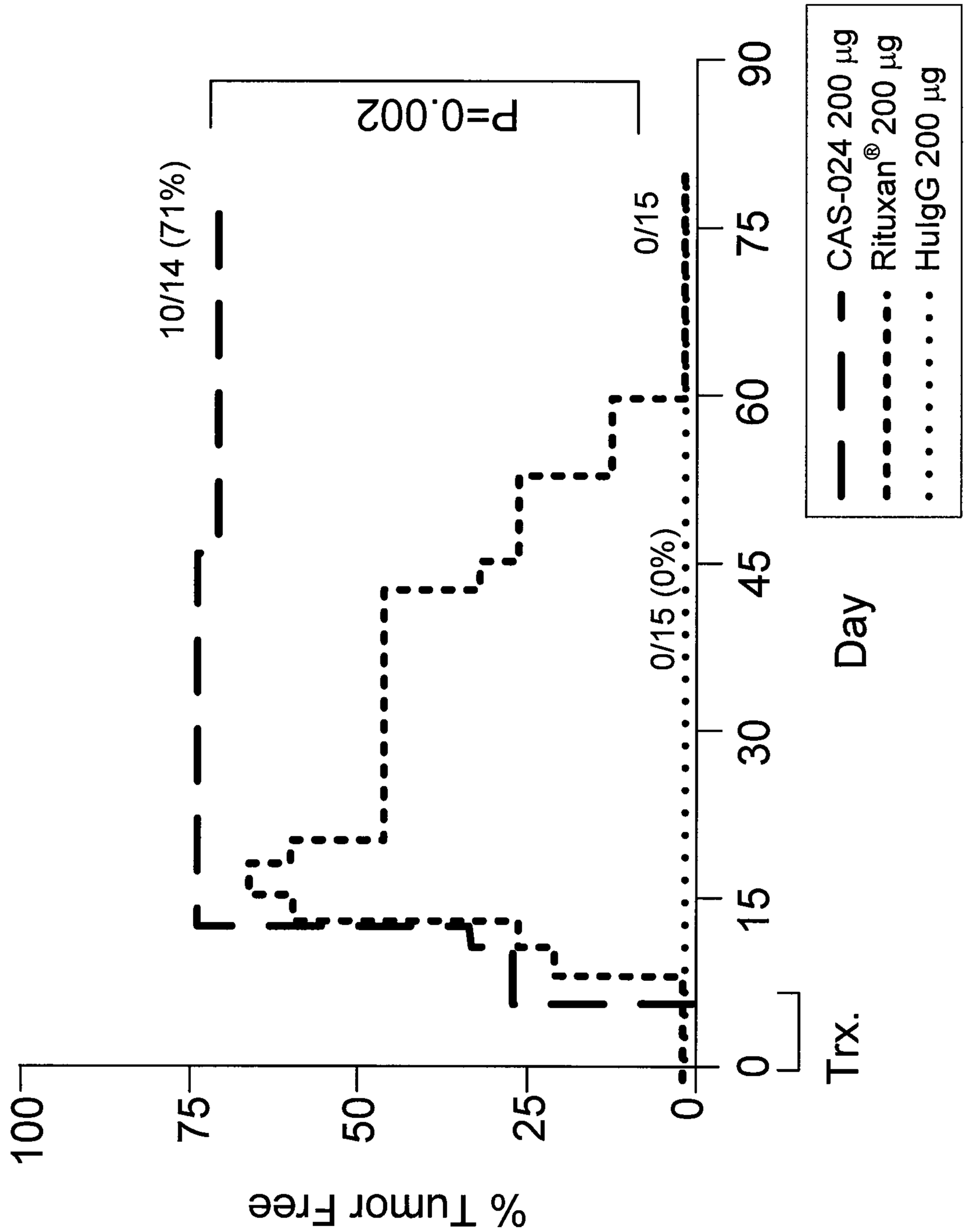
% Tumor Free
100
75
50
25
0
Trx.
0
15
30
45
60
75
90
Day
0/15 (0%)
0/15
10/14 (71%)
P=0.002
CAS-024 200 µg
Rituxan® 200 µg
HulgG 200 µg

Fig. 6B

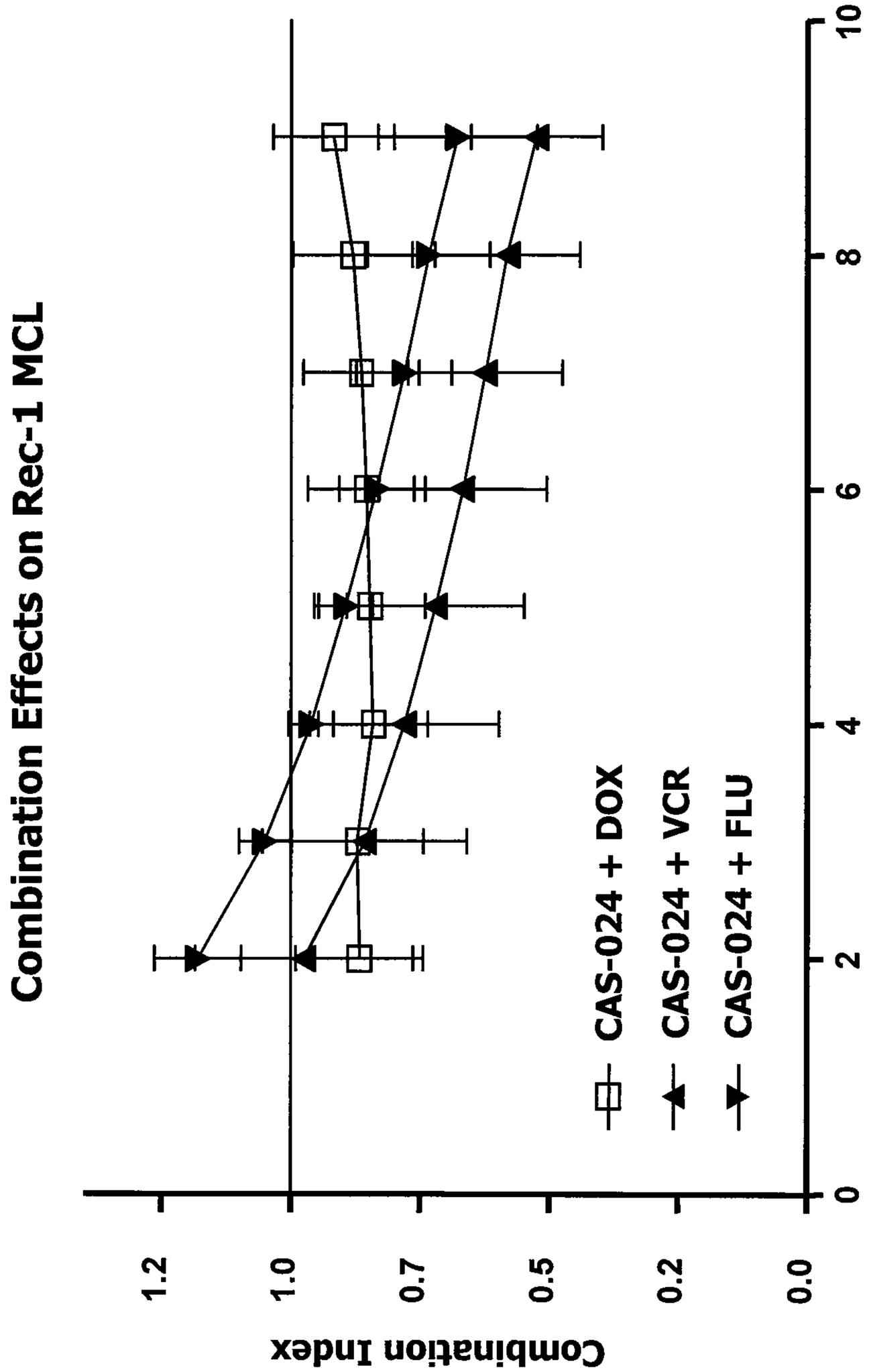
Combination Effect on Rec-1 MCL
Combination Index
1.2
1.0
0.7
0.5
0.2
0.0
0
2
4
6
8
10
Effect Level
CAS-024 + DOX
CAS-024 + VCR
CAS-024 + FLU

Fig. 7

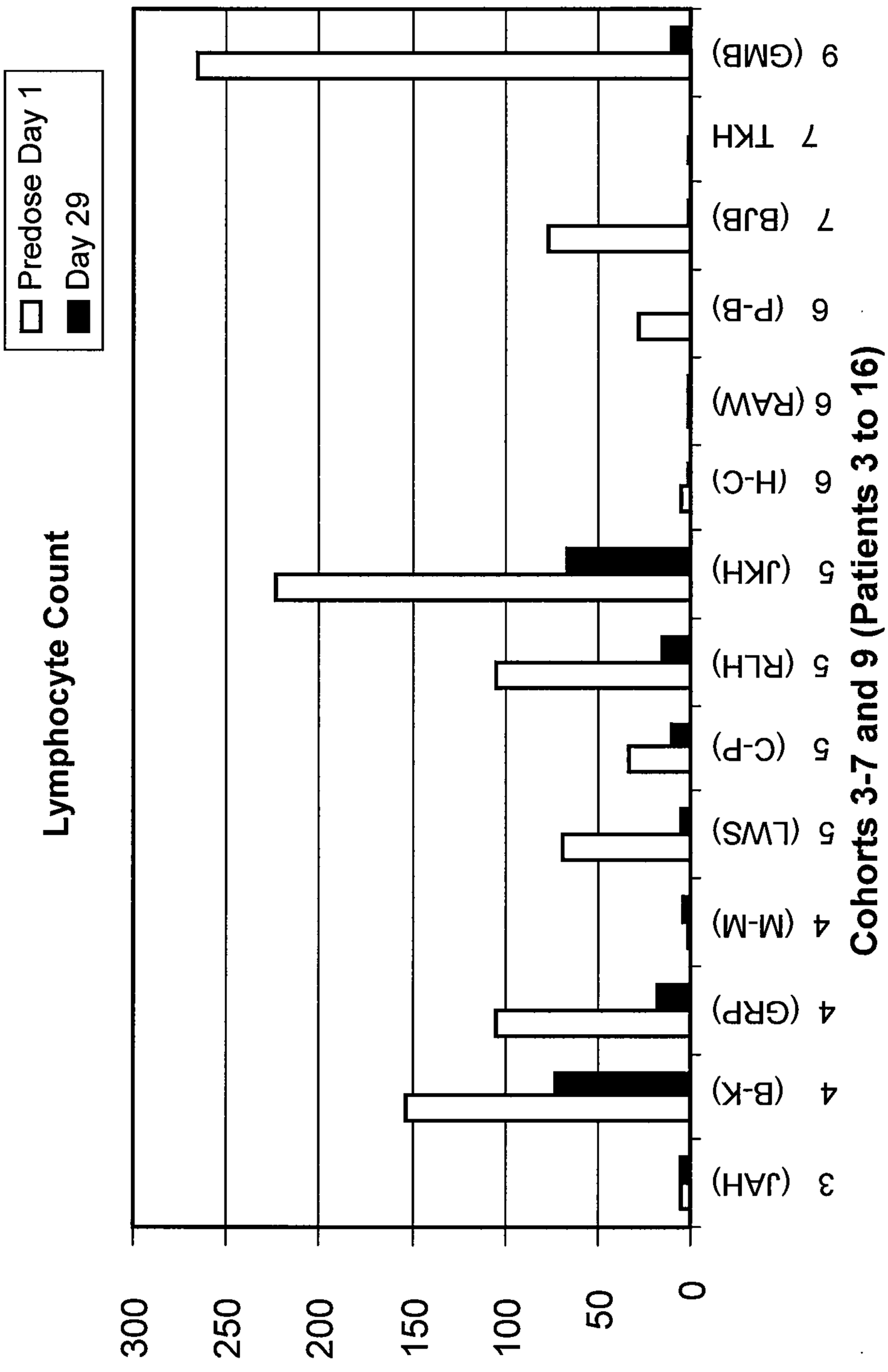
Predose Day 1
Day 29
Lymphocyte Count
Cohorts 3-7 and 9 (Patients 3 to 16)
Lymphocytes (x 1000)
300
250
200
150
100
50
0
3 (JAH)
4 (B-K)
4 (GRP)
4 (M-M)
5 (LWS)
5 (C-P)
5 (RLH)
5 (JKH)
6 (H-C)
6 (RAW)
6 (P-B)
7 (BJB)
7 TKH
9 (GMB)

Fig. 8

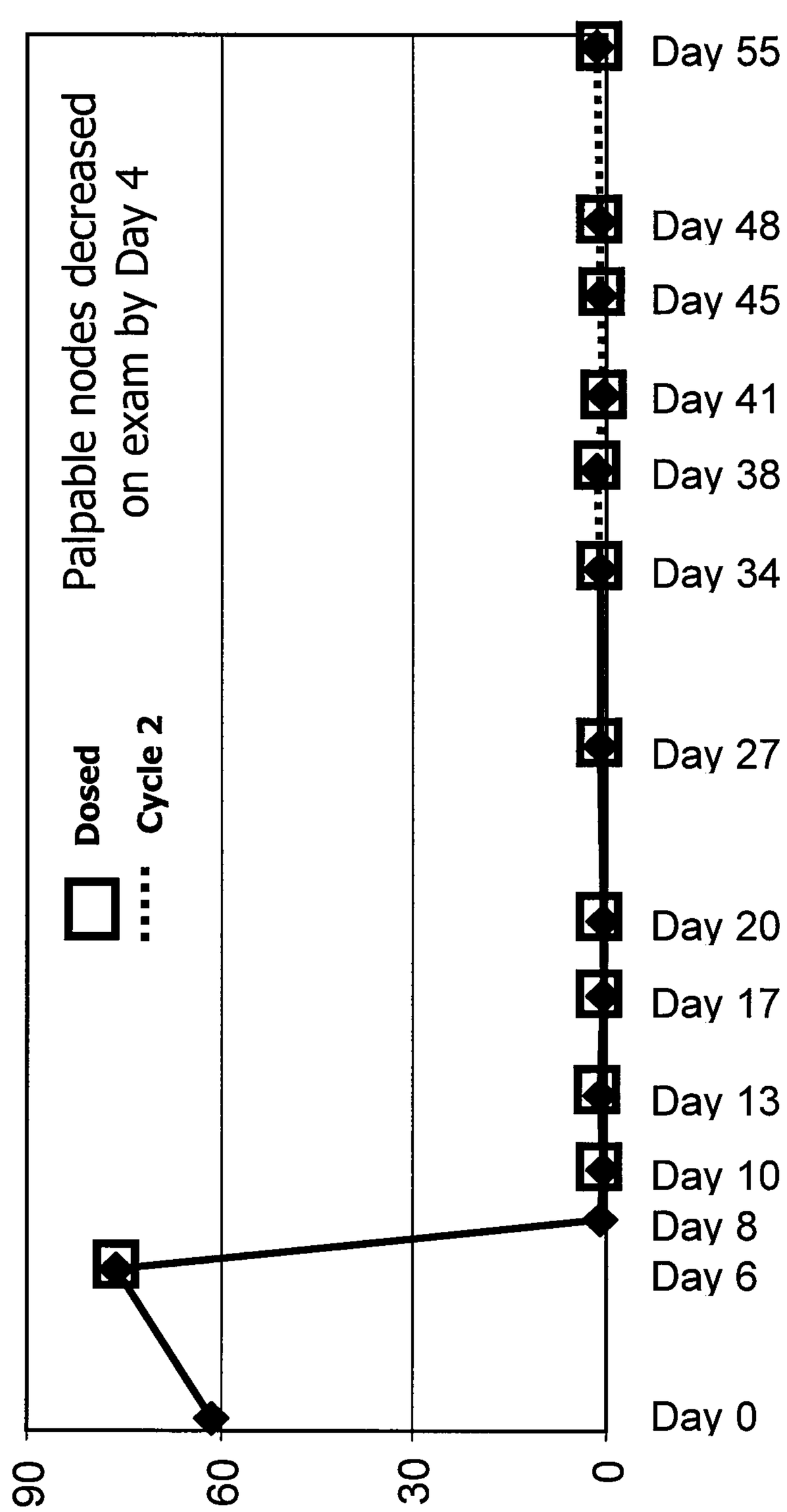
Patient BJB
Palpable nodes decreased on exam by Day 4
Dosed
Cycle 2
Day 55
Day 48
Day 45
Day 41
Day 38
Day 34
Day 27
Day 20
Day 17
Day 13
Day 10
Day 8
Day 6
Day 0
90
60
30
0
Lymphocytes count (x 10³/uL)

Fig. 9

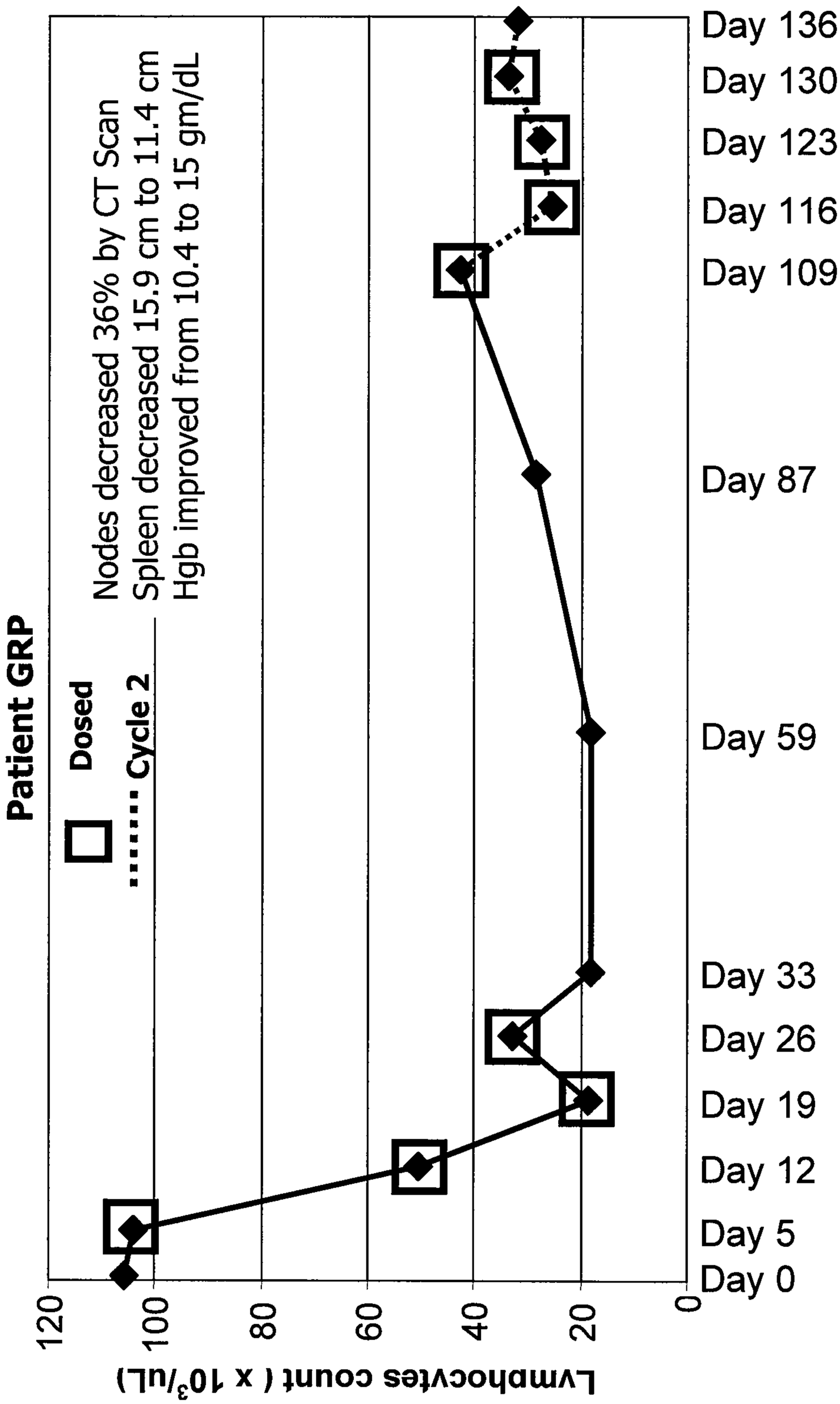
Patient GRP
Dosed
Cycle 2
Nodes decreased 36% by CT S
Spleen decreased 15.9 cm to 1
Hgb improved from 10.4 to 15
Day 136
Day 130
Day 123
Day 116
Day 109
Day 87
Day 59
Day 33
Day 26
Day 19
Day 12
Day 5
Day 0
120
100
80
60
40
20
0
Lymphocytes count (x 10³/uL)

Fig. 10

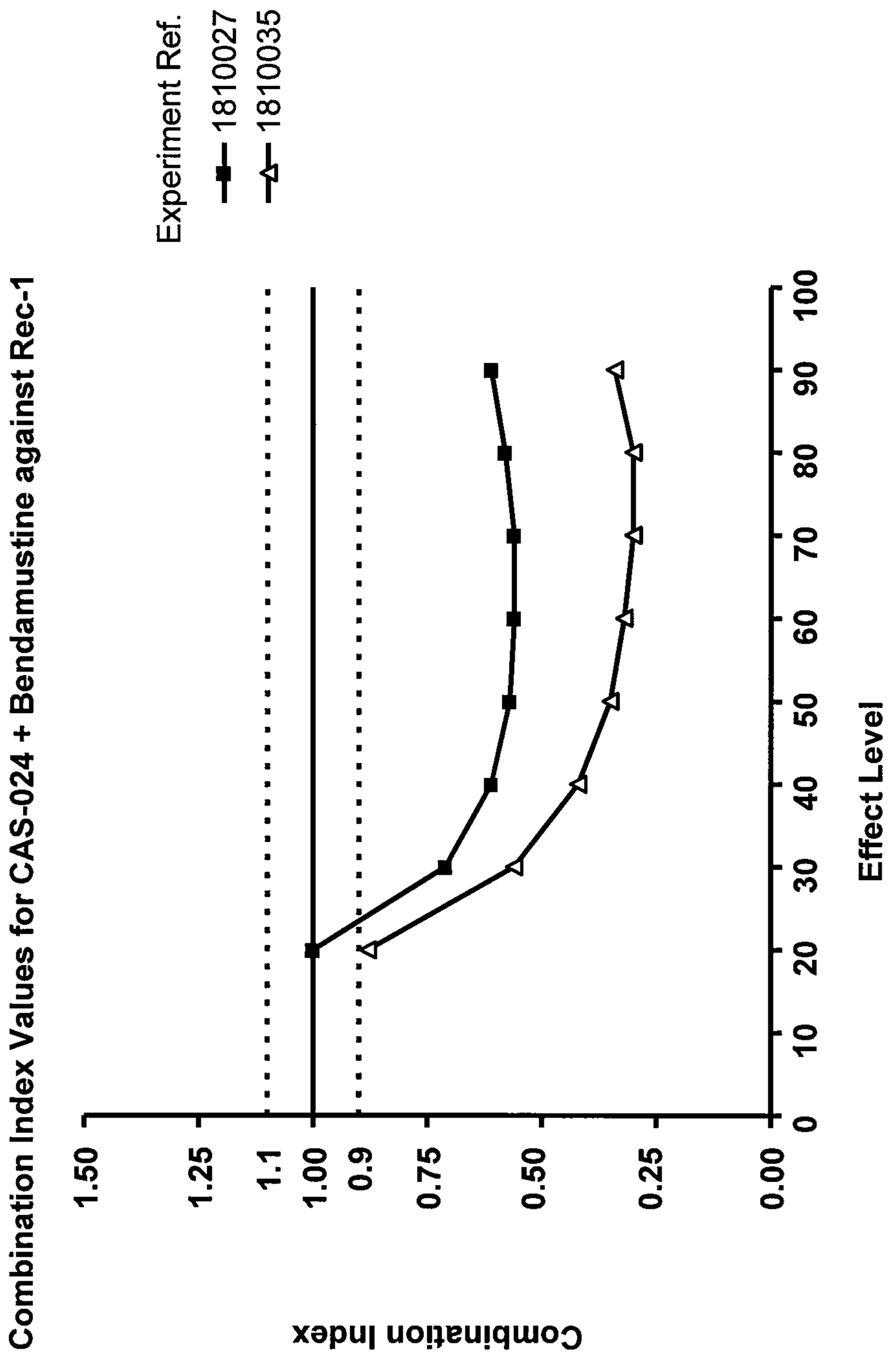
Combination Index Values for CAS-024 + Bendamustine against Rec-1
1.50
1.25
1.1
1.00
0.9
0.75
0.50
0.25
0.00
0
10
20
30
40
50
60
70
80
90
100
Effect Level
Combination Index
Experiment Ref.
181027
181035

Fig. 11

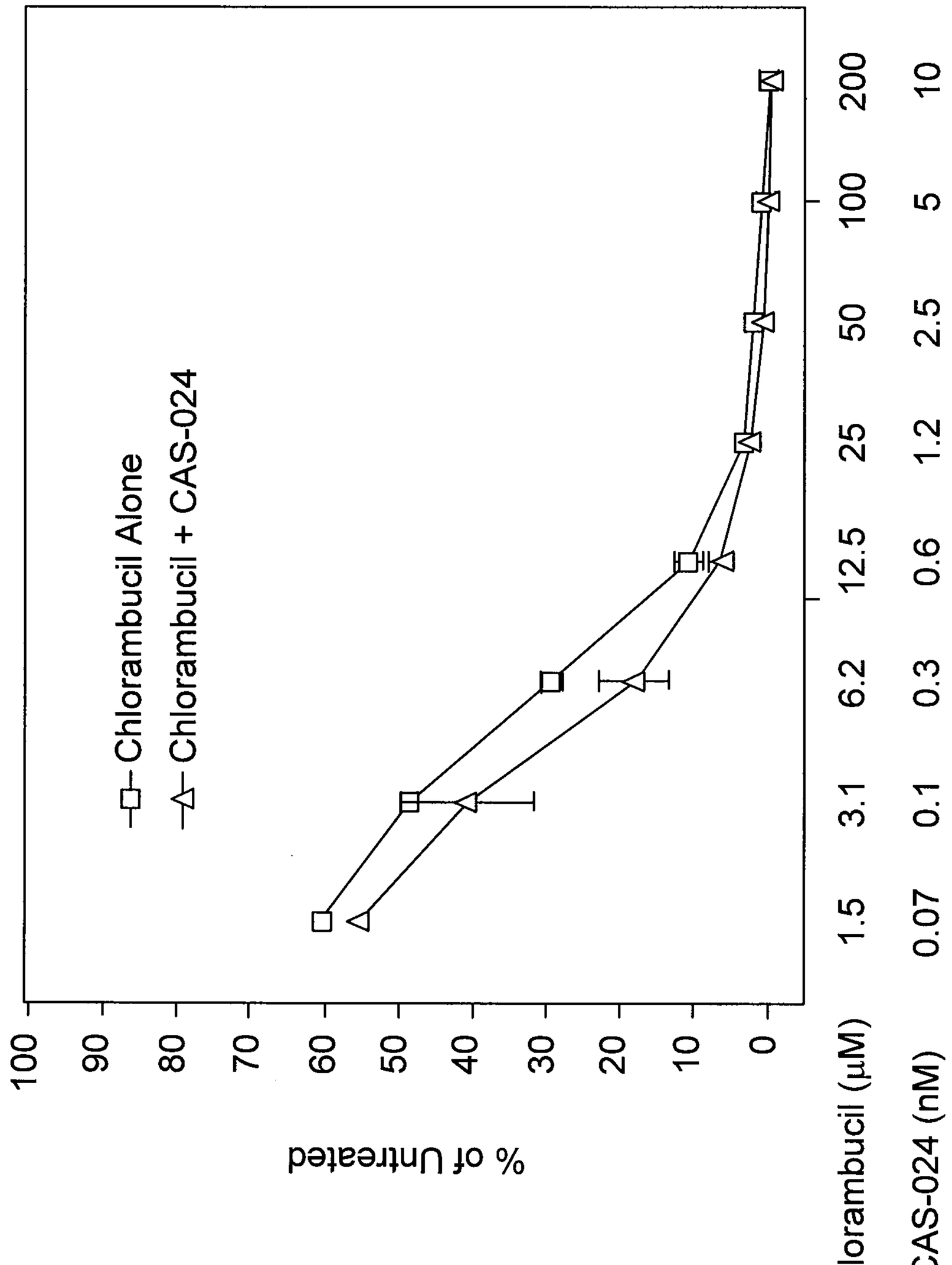
Activity vs SU-DHL-6
Chlorambucil Alone
Chlorambucil + CAS-024
% of Untreated
100
90
80
70
60
50
40
30
20
10
0
Chlorambucil (μM)
1.5
3.1
6.2
12.5
25
50
100
200
CAS-024 (nM)
0.07
0.1
0.3
0.6
1.2
2.5
5
10

Fig. 12

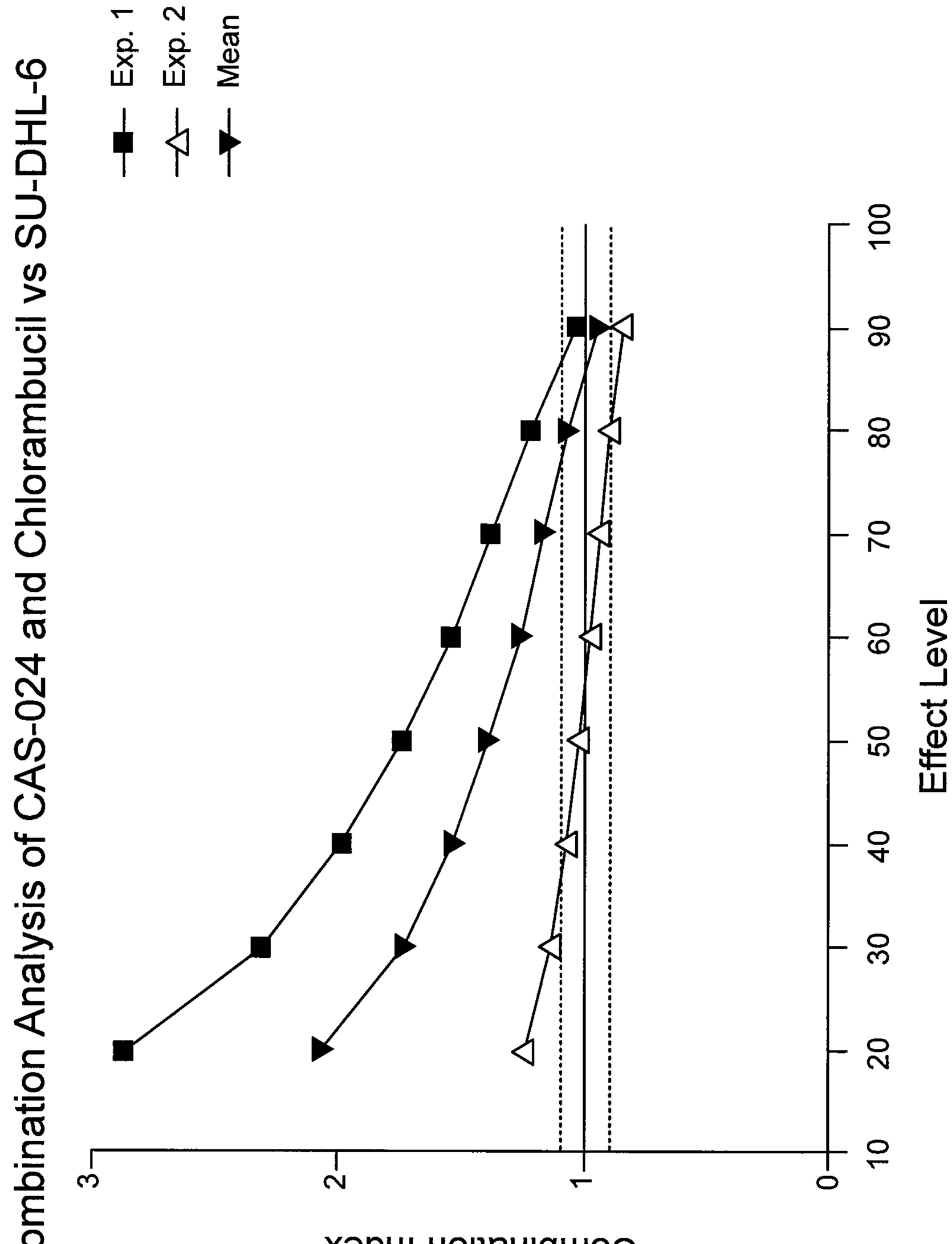
CAS-024-6
Exp. 1
Exp. 2
Mean
Combination Analysis of CAS-024 and Chlorambucil vs SU-DHL
Combination Index
0
1
2
3
10
20
30
40
50
60
70
80
90
100
Effect Level

Fig. 13

Comparison in Kruskal-Wallis test with Dunn's Multiple Comparison Post-test	p value
hulgG vs CAS-024	< 0.001
hulgG vs Bendamustine	< 0.05
hulgG vs CAS-024+Bendamustine	< 0.001
CAS-024 vs Bendamustine	> 0.05
CAS-024 vs CAS-024+Bendamustine	> 0.05
Bendamustine vs CAS-024+ Bendamustine	< 0.01

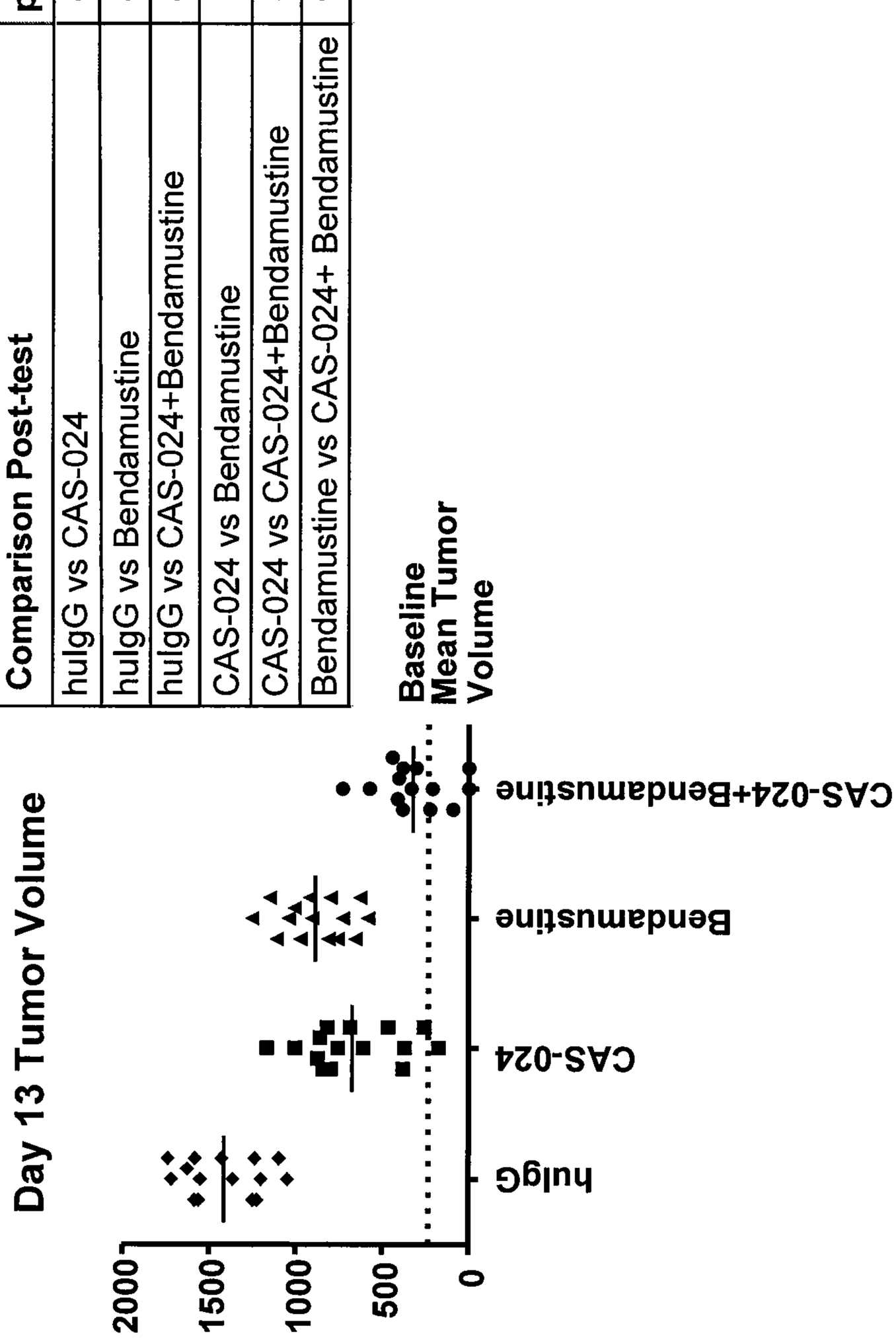

Fig. 14A

Comparison in Kruskal-Wallis test with Dunn's Multiple Comparison Post-test	p value
hulgG vs CAS-024	< 0.001
hulgG vs Bendamustine	< 0.05
hulgG vs CAS-024+Bendamustine	< 0.001
CAS-024 vs Bendamustine	> 0.05
CAS-024 vs CAS-024+Bendamustine	> 0.05
Bendamustine vs CAS-024+ Bendamustine	< 0.01

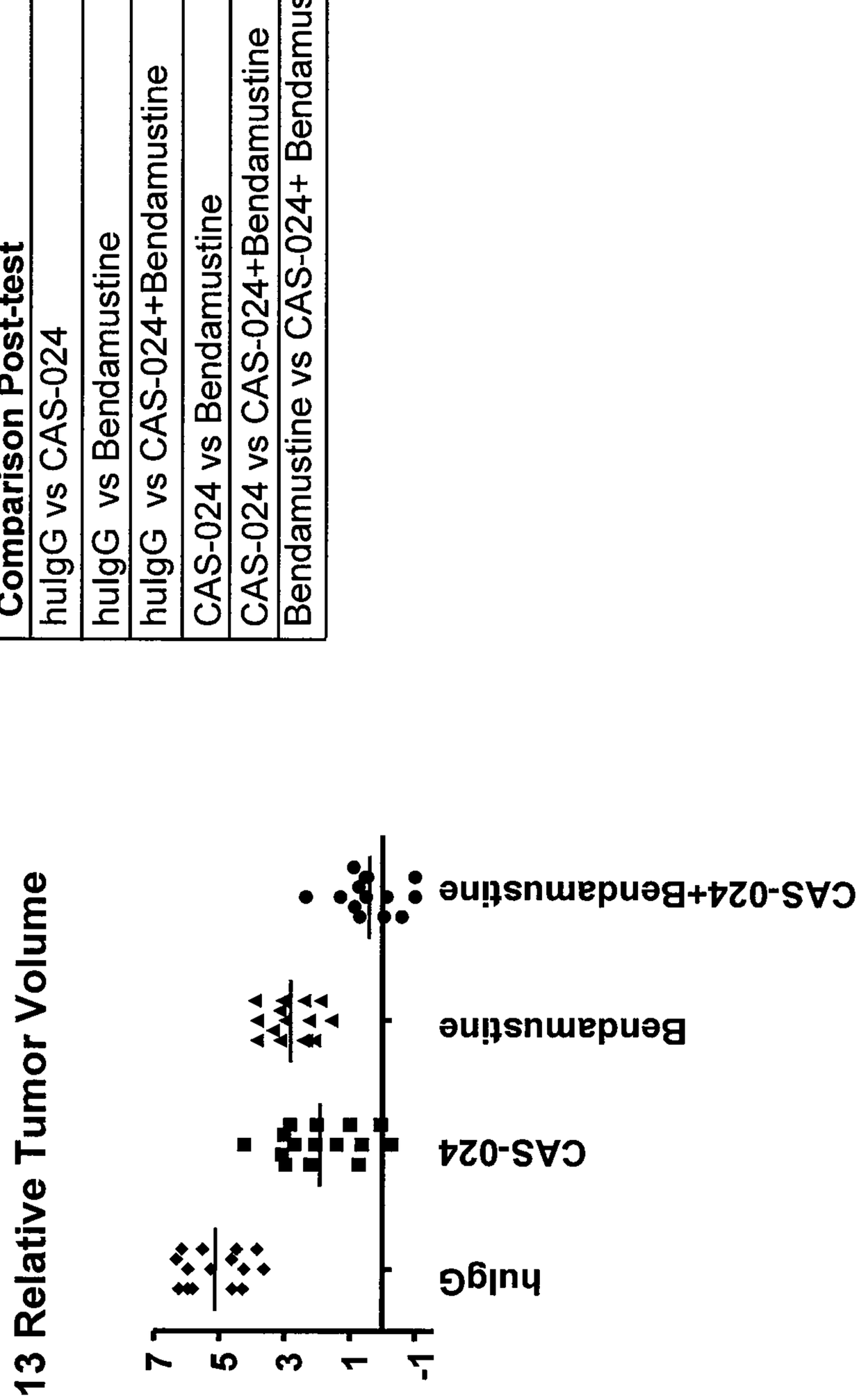

Fig. 14B

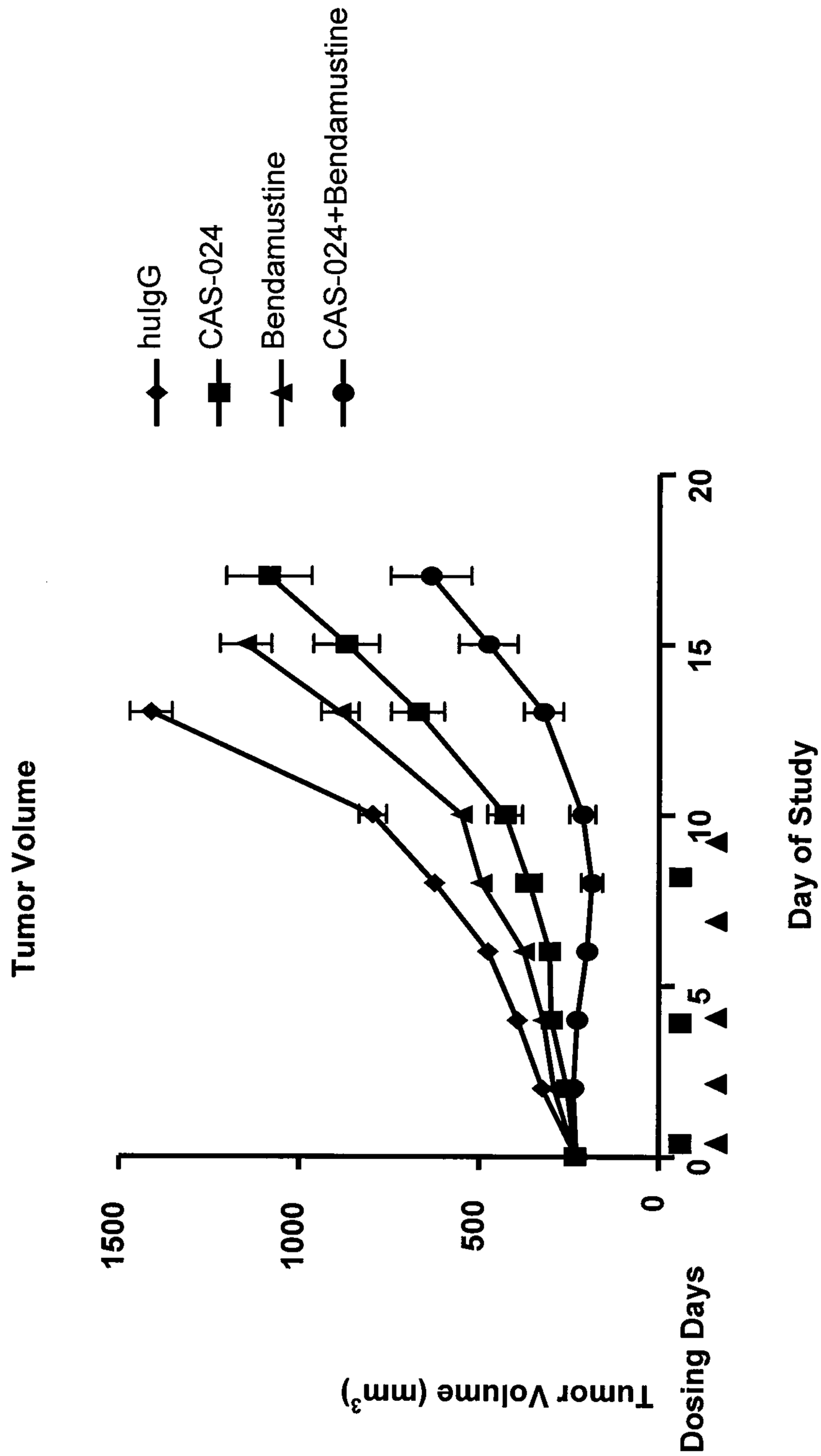
huIgG
CAS-024
Bendamustine
CAS-024+Bendamustine
Tumor Volume
1500
1000
500
0
0
5
10
15
20
Day of Study
Tumor Volume (mm³)
Dosing Days

Fig. 15

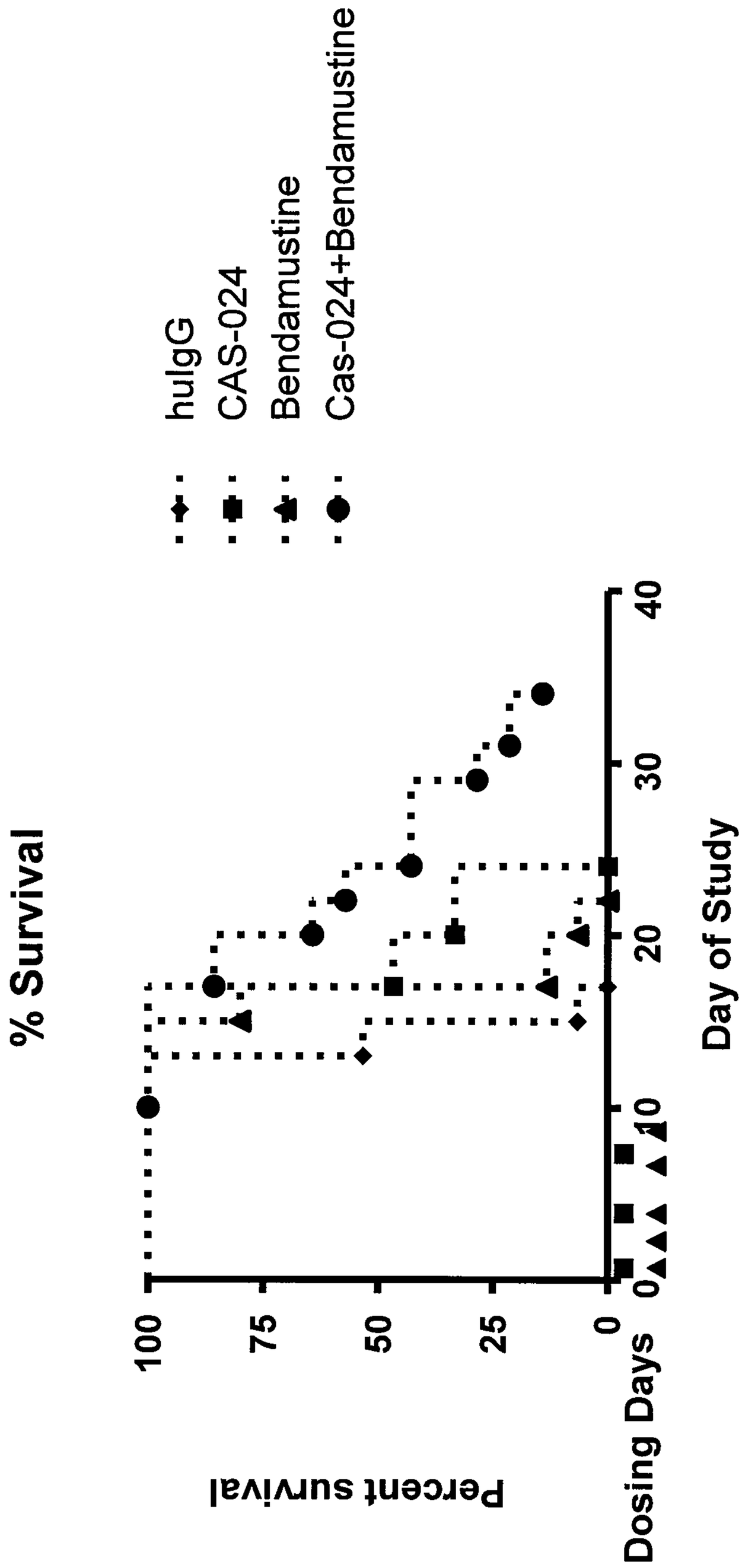
huIgG
CAS-024
Bendamustine
Cas-024+Bendamustine
% Survival
Day of Study
Percent survival
Dosing Days
100
75
50
25
0
0
10
20
30
40

Fig. 16

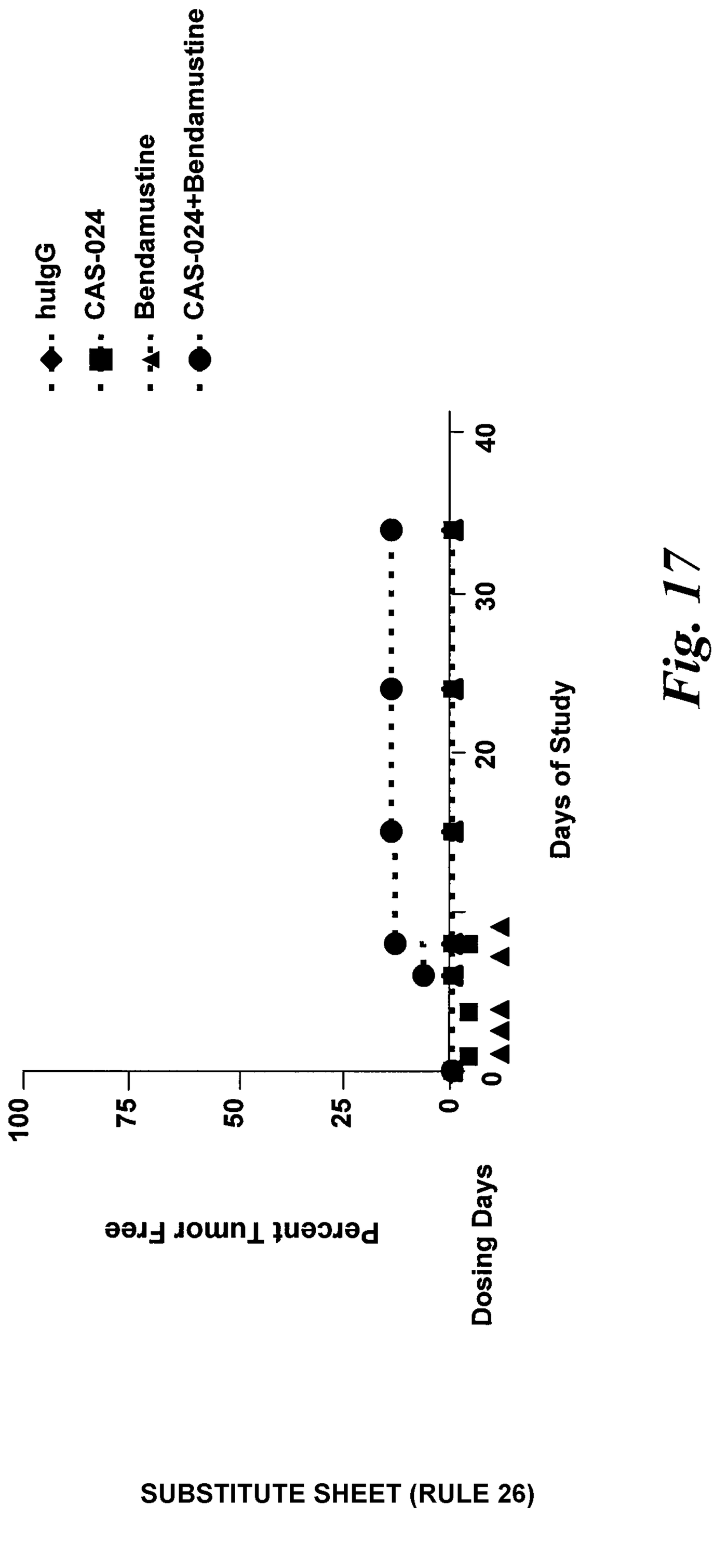
hulgG
CAS-024
Bendamustine
CAS-024+Bendamustine
% Tumor Free
Days of Study
Percent Tumor Free
Dosing Days
100
75
50
25
0
0
20
30
40

Fig. 17

HEAVY CHAIN

	FR1	CDR1	FR2	CDR2
G28-1	AVQLQQSGPESEKPGASVKISCKASGYSFT	GYNMN	WVKQNNGKSLEWIG	NIDPYYGGTTYNRKFKG
CAS-024	EVQLVQSGAEVKKPGESLKISCKGSGYSFT	GYNMN	WVRQMPGKGLEWMG	NIDPYYGGTTYNRKFKG
Consensus	-VQL-QSG-E--KPG-S-KISCK-SGYSFT	GYNMN	WV-Q--GK-LEW-G	NIDPYYGGTTYNRKFKG

	FR3	CDR3	FR4
G28-1	KATLTVDKSSSTAYMQLKSLTSEDSAVYYCAR	SVGPMDY	WGQGTSVTVSS
CAS-024	QVTISADKSISTAYLQWSSLKASDTAMYYCAR	SVGPFDS	WGQGTLVTVSS
Consensus	--T---DKS-STAY-Q--SL---D-A-YYCAR	SVGP-D-	WGQGT-VTVSS

LIGHT CHAIN

	FR1	CDR1	FR2	CDR2
G28-1	DIQMTQSPASLSASVGETVTITC	RTSENVYSYLA	WYQQKQGKSPQLLVS	FAKTLAE
CAS-024	EIVLTQSPATLSLSPGERATLSC	RASENVYSYLA	WYQQKPGQAPRLLIY	FAKTLAE
Consensus	-I--TQSPATLS-S-GE--T--C	R-SENVYSYLA	WYQQK-G--P-LL--	FAKTLAE

	FR3	CDR3	FR4
G28-1	GVPSRFSGSGSGTQFSLKISSLQPEDSGSYFC	QHHSDNPWT	FGGGTELEIK
CAS-024	GIPARFSGSGSGTDFTLTISSLEPEDFAVYYC	QHHSDNPWT	FGQGTKVEIK
Consensus	G-P-RFSGSGSGT-F-L-ISSL-PED---Y-C	QHHSDNPWT	FG-GT--EIK