Antitumor combinations containing antibodies recognizing specifically CD38 and melphalan.

The present invention relates to combinations of monoclonal antibodies directed against CD38 and melphalan which are therapeutically useful in the treatment of neoplastic diseases.

CD38 is a 45 kD type II transmembrane glycoprotein with a long C-terminal extracellular domain and a short N-terminal cytoplasmic domain. The CD38 protein is a bifunctional ectoenzyme that can catalyze the conversion of NAD^+ into cyclic ADP-ribose (cADPR) and also hydrolyze cADPR into ADP-ribose. CD38 is upregulated and has been implicated in many hematopoietic malignancies.

Monoclonal antibodies 38SB13, 38SB18, 38SB19, 38SB30, 38SB31, and 38SB39, which specifically recognize CD38, are described in PCT application WO2008/047242. Said anti-CD38 antibodies are capable of killing $CD38^+$ cells by three different cytotoxic mechanisms, induction of apoptosis, antibody-dependent cell-mediated cytotoxicity (ADCC), and complement-dependent cytotoxicity (CDC). In addition, these antibodies are able to directly induce apoptosis of $CD38^+$ cells, even without the presence of stroma cells or stroma-derived cytokines. Melphalan is an alkylating agent used in chemotherapy. Nevertheless, there is still a need for new and efficacious medicaments for treating cancer.

It has now been found, and for this invention, that the efficacy of the humanized anti-CD38 antibodies may be considerably improved when it is administered in combination with at least one substance which is therapeutically useful in anticancer treatments and has a mechanism identical to or different from the one of the humanized anti-CD38 antibodies and which is limited in the present invention to melphalan.

The term "antibody" is used herein in the broadest sense and specifically covers monoclonal antibodies (including full length monoclonal antibodies) of any isotype such as IgG, IgM, IgA, IgD and IgE, polyclonal antibodies, multispecific antibodies, chimeric antibodies, and antibody fragments. A typical IgG antibody is comprised of two identical heavy chains and two identical light chains that are joined by disulfide bonds. Each heavy and light chain contains a constant region and a variable region. Each variable region contains three segments called "complementarity-determining regions" ("CDRs")

or "hypervariable regions", which are primarily responsible for binding an epitope of an antigen. They are usually referred to as CDR1, CDR2, and CDR3, numbered sequentially from the N-terminus. The more highly conserved portions of the variable regions outside of the CDRs are called the "framework regions".

As used herein, "V_H" or "VH" refers to the variable region of an immunoglobulin heavy chain of an antibody, including the heavy chain of an Fv, scFv, dsFv, Fab, Fab' or F(ab')2 fragment. Reference to "V_L" or "VL" refers to the variable region of the immunoglobulin light chain of an antibody, including the light chain of an Fv, scFv, dsFv, Fab, Fab' or F(ab')2 fragment.

The 38SB13 antibody comprises at least one heavy chain having an amino acid sequence consisting of SEQ ID NO: 50 and at least one light chain having an amino acid sequence consisting of SEQ ID NO: 38, said heavy chain comprising three sequential CDRs having amino acid sequences consisting of SEQ ID NOS: 1, 2, and 3, and said light chain comprising three sequential CDRs having amino acid sequences consisting of SEQ ID NOS: 4, 5, and 6.

The 38SB18 antibody comprises at least one heavy chain having an amino acid sequence consisting of SEQ ID NO: 52 and at least one light chain having an amino acid sequence consisting of SEQ ID NO: 40, said heavy chain comprising three sequential CDRs having amino acid sequences consisting of SEQ ID NOS: 7, 8, and 9, and said light chain comprising three sequential CDRs having amino acid sequences consisting of SEQ ID NOS: 10, 11, and 12.

The 38SB19 antibody comprises at least one heavy chain having an amino acid sequence consisting of SEQ ID NO: 54 and at least one light chain having an amino acid sequence consisting of SEQ ID NO: 42, said heavy chain comprising three sequential CDRs having amino acid sequences consisting of SEQ ID NOS: 13, 14, and 15, and said light chain comprising three sequential CDRs having amino acid sequences consisting of SEQ ID NOS: 16, 17, and 18.

The 38SB30 antibody comprises at least one heavy chain having an amino acid sequence consisting of SEQ ID NO: 56 and at least one light chain having an amino acid sequence consisting of SEQ ID NO: 44, said heavy chain comprising three sequential CDRs having amino acid sequences consisting of SEQ ID NOS: 19, 20, and

21, and said light chain comprising three sequential CDRs having amino acid sequences consisting of SEQ ID NOS: 22, 23, and 24.

The 38SB31 antibody comprises at least one heavy chain having an amino acid sequence consisting of SEQ ID NO: 58 and at least one light chain having an amino acid sequence consisting of SEQ ID NO: 46, said heavy chain comprising three sequential CDRs having amino acid sequences consisting of SEQ ID NOS: 25, 26, and 27, and said light chain comprising three sequential CDRs having amino acid sequences consisting of SEQ ID NOS: 28, 29, and 30.

The 38SB39 antibody comprises at least one heavy chain having an amino acid sequence consisting of SEQ ID NO: 60 and at least one light chain having an amino acid sequence consisting of SEQ ID NO: 48, said heavy chain comprising three sequential CDRs having amino acid sequences consisting of SEQ ID NOS: 31, 32, and 33, and said light chain comprising three sequential CDRs having amino acid sequences consisting of SEQ ID NOS: 34, 35, and 36.

The hybridoma cell lines producing the 38SB13, 38SB18, 38SB19, 38SB30, 38SB31, and 38SB39 murine anti-CD38 antibodies have been deposited at the American Type Culture Collection (10801 University Bld, Manassas, VA, 20110-2209, USA), on June 21, 2006, under the deposit numbers PTA-7667, PTA-7669, PTA-7670, PTA-7666, PTA-7668, and PTA-7671, respectively (as described in WO2008/047242).

The term "humanized antibody", as used herein, refers to a chimeric antibody which contain minimal sequence derived from non-human immunoglobulin. The goal of humanization is a reduction in the immunogenicity of a xenogenic antibody, such as a murine antibody, for introduction into a human, while maintaining the full antigen binding affinity and specificity of the antibody. Humanized antibodies, or antibodies adapted for non-rejection by other mammals, may be produced using several technologies such as resurfacing and CDR grafting. As used herein, the resurfacing technology uses a combination of molecular modelling, statistical analysis and mutagenesis to alter the non-CDR surfaces of antibody variable regions to resemble the surfaces of known antibodies of the target host. The CDR grafting technology involves substituting the complementarity determining regions of, for example, a mouse antibody, into a human framework domain, e.g., see W0 92/22653. Humanized chimeric antibodies preferably have constant regions and variable regions other than

the complementarity determining regions (CDRs) derived substantially or exclusively from the corresponding human antibody regions and CDRs derived substantially or exclusively from a mammal other than a human.

Strategies and methods for the resurfacing of antibodies, and other methods for reducing immunogenicity of antibodies within a different host, are disclosed in US Patent 5,639,641, which is hereby incorporated in its entirety by reference. Antibodies can be humanized using a variety of other techniques including CDR-grafting (EP 0 239 400; WO 91/09967; U.S. Pat. Nos. 5,530,101; and 5,585,089), veneering or resurfacing (EP 0 592 106; EP 0 519 596; Padlan E. A., 1991, *Molecular Immunology* **28(4/5)**: 489-498; Studnicka G. M. *et al.*, 1994, *Protein Engineering*, **7(6)**: 805-814; Roguska M.A. *et al.*, 1994, *PNAS*, **91**: 969-973), chain shuffling (U.S. Pat. No. 5,565,332), and identification of flexible residues (PCT/US2008/074381). Human antibodies can be made by a variety of methods known in the art including phage display methods. See also U.S. Pat. Nos. 4,444,887, 4,716,111, 5,545,806, and 5,814,318; and international patent application publication numbers WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO 96/34096, WO 96/33735, and WO 91/10741 (said references incorporated by reference in their entireties).

The anti-CD38 antibodies of the pharmaceutical combination of the present invention are humanized antibodies which recognize CD38 and kill $CD38^+$ cells by apoptosis, ADCC, and CDC. In a further embodiment, the humanized antibodies of the invention are capable of killing said $CD38^+$ cells by apoptosis even in the absence of stroma cells or stroma-derived cytokines.

A preferred embodiment of such a humanized antibody is a humanized 38SB13, 38SB18, 38SB19, 38SB30, 38SB31, or 38SB39 antibody, or an epitope-binding fragment thereof.

The CDRs of the 38SB13, 38SB18, 38SB19, 38SB30, 38SB31, and 38SB39 antibodies are identified by modelling and their molecular structures have been predicted. Thus, in one embodiment, this invention provides humanized antibodies or epitope-binding fragment thereof comprising one or more CDRs having an amino acid sequence selected from the group consisting of SEQ ID NOS: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, and 36. In a preferred embodiment, a humanized version of 38SB13 is provided, which

comprises at least one heavy chain and at least one light chain, wherein said heavy chain comprises three sequential complementarity-determining regions having amino acid sequences represented by SEQ ID NOS: 1, 2, and 3, and wherein said light chain comprises three sequential complementarity-determining regions having amino acid sequences represented by SEQ ID NOS: 4, 5, and 6. In another preferred embodiment, a humanized version of 38SB18 is provided, which comprises at least one heavy chain and at least one light chain, wherein said heavy chain comprises three sequential complementarity-determining regions having amino acid sequences represented by SEQ ID NOS: 7, 8, and 9, and wherein said light chain comprises three sequential complementarity-determining regions having amino acid sequences represented by SEQ ID NOS: 10, 11, and 12. In another preferred embodiment, a humanized version of 38SB19 is provided, which comprises at least one heavy chain and at least one light chain, wherein said heavy chain comprises three sequential complementarity-determining regions having amino acid sequences represented by SEQ ID NOS: 13, 14, and 15, and wherein said light chain comprises three sequential complementarity-determining regions having amino acid sequences represented by SEQ ID NOS: 16, 17, and 18. In another preferred embodiment, a humanized version of 38SB30 is provided, which comprises at least one heavy chain and at least one light chain, wherein said heavy chain comprises three sequential complementarity-determining regions having amino acid sequences represented by SEQ ID NOS: 19, 20, and 21, and wherein said light chain comprises three sequential complementarity-determining regions having amino acid sequences represented by SEQ ID NOS: 22, 23, and 24. In another preferred embodiment, a humanized version of 38SB31 is provided, which comprises at least one heavy chain and at least one light chain, wherein said heavy chain comprises three sequential complementarity-determining regions having amino acid sequences represented by SEQ ID NOS: 25, 26, and 27, and wherein said light chain comprises three sequential complementarity-determining regions having amino acid sequences represented by SEQ ID NOS: 28, 29, and 30. In another preferred embodiment, a humanized version of 38SB39 is provided, which comprises at least one heavy chain and at least one light chain, wherein said heavy chain comprises three sequential complementarity-determining regions having amino acid sequences represented by SEQ ID NOS: 31, 32, and 33, and wherein said light chain comprises three sequential complementarity-determining regions having amino acid sequences represented by SEQ ID NOS: 34, 35, and 36.

In one embodiment, this invention provides humanized antibodies or fragments thereof which comprise a V_H having an amino acid sequence selected from the group of SEQ ID NOS: 66 and 72. In a preferred embodiment, a humanized 38SB19 antibody is provided which comprises a V_H having an amino acid sequence represented by SEQ ID NO: 66. In another preferred embodiment, a humanized 38SB31 antibody is provided which comprises a V_H having an amino acid sequence represented by SEQ ID NO: 72.

In another embodiment, this invention provides humanized antibodies or fragments thereof which comprise a V_L having an amino acid sequence selected from the group of SEQ ID NOS: 62, 64, 68, and 70. In a preferred embodiment, a humanized 38SB19 antibody is provided which comprises a V_L having an amino acid sequence chosen from the group of SEQ ID NOS: 62 and 64. In another preferred embodiment, a humanized 38SB31 antibody is provided which comprises a V_L having an amino acid sequence chosen from the group of SEQ ID NOS: 68 and 70.

Each of the humanized versions of the 38SB13, 38SB18, 38SB19, 38SB30, 38SB31, and 38SB39 antibodies has been shown to be particularly advantageous as an anticancer agent. The preparation, physical properties and beneficial pharmacological properties thereof are described in WO 2008/047242, which is incorporated by reference herein in its entirety. Generally, the doses used for treating human beings, which depend on factors distinctive to the subject to be treated, are between 1 and 150 mg/kg administered orally or between 1 and 150 mg/kg administered intravenously.

Melphalan (brand name, Alkeran™), is a chemotherapy drug belonging to the class of nitrogen mustard alkylating agents. Otherwise known as L-Phenylalanine Mustard, or L-PAM, melphalan is a phenylalanine derivative of mechlorethamine and is a bifunctional alkylating agent. Formation of carbonium intermediates from each of the two bis-2-chloroethyl groups enables alkylation through covalent binding with the 7-nitrogen of guanine on DNA, cross-linking two DNA strands and thereby preventing cell replication. Melphalan is used primarily to treat multiple myeloma and ovarian cancer, and occasionally malignant melanoma. It is usually administered orally or intravenously.

One aspect of the invention is a pharmaceutical composition comprising an anti-CD38 antibody in combination with at least melphalan. Since the activity of the products depends on the doses used, it is thus possible to use lower doses and to increase the

activity while decreasing the toxicity phenomena. The improved efficacy of a combination according to the invention may be demonstrated by determination of the therapeutic synergy. A combination manifests therapeutic synergy if it is therapeutically superior to the best agent of the study used alone at its maximum tolerated dose or at its highest dose tested when toxicity cannot be reached in the animal species.

This efficacy may be quantified, for example, by the $\log_{10}$ cells kill, which is determined according to the following formula:

$$\log_{10} \text{ cell kill} = \text{T-C (days)}/3.32\times T_d$$

in which T - C represents the tumor growth delay, which is the median time in days for the tumors of the treated group (T) and the tumors of the control group (C) to reach a predetermined value (1 g for example), and T_d represents the time in days needed for the volume of the tumor to double in the control animals [T.H. Corbett et al., *Cancer*, **40**: 2660-2680 (1977); F.M. Schabel et al., *Cancer Drug Development*, Part B, Methods in Cancer Research, **17**: 3-51, New York, Academic Press Inc. (1979)]. A product is considered to be active if $\log_{10}$ cell kill is greater than or equal to 0.7. A product is considered to be very active if $\log_{10}$ cell kill is greater than 2.8.

The combination will manifest therapeutic synergy when the $\log_{10}$ cell kill is greater than the value of the $\log_{10}$ cell kill of the best constituent when it is administered alone and used at its maximum tolerated dose or at its highest dose tested.

The efficacy of the combinations on solid tumors may be determined experimentally in the following manner:

The animals subjected to the experiment, generally mice, are subcutaneously grafted bilaterally with 30 to 60 mg of a tumor fragment on day 0. The animals bearing tumors are randomized based on their tumor size before being subjected to the various treatments and controls. Chemotherapy begins when tumors have reached a predetermined size after grafting, depending on the type of tumor, and the animals are observed every day. The different animal groups are weighed daily during treatment until the maximum weight loss is reached and subsequent full weight recovery has occurred. The groups are then weighed once or twice a week until the end of the trial.

The tumors are measured 1 to 5 times a week, depending on the tumor doubling time, until the tumor reaches approximately 2 g, or until the animal dies (if this occurs before the tumor reaches 2 g). The animals are necropsied immediately after euthanasia or death.

The antitumor activity is determined in accordance with the different parameters recorded.

Results obtained with combinations of hu38SB19 and melphalan used at their optimal doses are indicated hereunder as examples.

The present invention also relates, therefore, to pharmaceutical compositions containing the combinations according to the invention.

The constituents of which the combination are composed may be administered simultaneously, semi-simultaneously, separately, or spaced out over a period of time so as to obtain the maximum efficacy of the combination; it being possible for each administration to vary in its duration from a rapid administration to a continuous perfusion.

As a result, for the purposes of the present invention, the combinations are not exclusively limited to those which are obtained by physical association of the constituents, but also to those which permit a separate administration, which can be simultaneous or spaced out over a period of time.

The compositions according to the invention are preferably compositions which can be administered parentally. However, these compositions may be administered orally, subcutaneously or intraperitoneally in the case of localized regional therapies.

The compositions for parental administration are generally pharmaceutically acceptable, sterile solutions or suspensions which may optionally be prepared as required at the time of use. For the preparation of non-aqueous solutions or suspensions, natural vegetable oils such as olive oil, sesame oil or liquid petroleum or injectable organic esters such as ethyl oleate may be used. The sterile aqueous solutions can consist of a solution of the product in water. The aqueous solutions are suitable for intravenous administration provided the pH is appropriately adjusted and the solution is made

isotonic, for example with a sufficient amount of sodium chloride or glucose. The sterilization may be carried out by heating or by any other means which does not adversely affect the composition. The combinations may also take the form of liposomes or the form of an association with carriers as cyclodextrins or polyethylene glycols.

The compositions for oral, subcutaneous or intraperitoneal administration are preferably aqueous suspensions or solutions.

In the combinations according to the invention, the application of the constituents of which may be simultaneous, separate or spaced out over a period of time, it is especially advantageous for the amount of humanized anti-CD38 antibody to represent from 10 to 90 % by weight of the combination, it being possible for this content to vary in accordance with the nature of the associated substance, the efficacy sought and the nature of the cancer to be treated.

The combinations according to the invention are especially useful in the treatment of several types of cancers including (but not limited to) the following: carcinomas and adenocarcinomas, including that of the bladder, breast, colon, head-and-neck, prostate, kidney, liver, lung, ovary, pancreas, stomach, cervix, thyroid and skin, and including squamous cell carcinoma ; hematopoietic tumors of lymphoid lineage, including multiple myeloma, leukemia, acute and chronic lymphocytic (or lymphoid) leukemia, acute and chronic lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, non-Hodgkin lymphoma (e.g. Burkitt's lymphoma) ; hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous (myeloid or myelocytic) leukemias, and promyelocytic leukemia; tumors of mesenchymal origin, including fibrosarcoma, osteosarcoma and rhabdomyosarcoma; tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma, and schwannomas; and other tumors, including melanoma, teratocarcinoma, xeroderma pigmentosum, keratoacanthoma, and seminoma, and other cancers yet to be determined in which CD38 is expressed. They are mainly useful for treating leukemia, lymphoma and cancers resistant to the commonly used anticancer agents as the anti-CD38 antibodies of the invention have a unique mechanism of action.

Thus, the invention also encompasses the use of the above combinations for the manufacture of a medicament for the treatment of cancer.

Example:

In this example, the effectiveness of an anti-CD38 antibody/melphalan combination of the invention for tumor growth inhibition was demonstrated in vivo.

The first selected tumor model was a transplantable human multiple myeloma cell line, RPMI-8226, implanted in SCID mice.

Hu38SB19 was formulated in phosphate buffer saline without Ca^{2+} and Mg^{2+}, pH7.4. Hu38SB19 was administered intravenously on days 16, 19, 22, 25 after tumor implantation.

Melphalan was formulated in 5 % ethanol, 5 % polysorbate 80, 90 % sodium chloride 0.9 % in water. Melphalan was administered intravenously simultaneously to hu38SB19 on days 16, 19, 22, 25 after tumor implantation (except for the highest dose of the combination for which treatment was stopped on day 19 when toxicity was reached).

The results of the experiment are reported in Table 1.

Tumor doubling time = 3.2 days.

The following end points have been used:

- Toxicity was declared at dosages inducing ≥ 20 % body weight loss or ≥ 10 % drug death,
- Antitumor efficacy was determined by calculating log10 cell kill = (T-C) / [3.32 x (tumor doubling time in days)]
  (T meaning the median time of the treated mice to reach 1000 mg and C the median time (25.3 days) of the control mice to reach the same size; tumor-free survivors are excluded from these calculations and are tabulated separately). No antitumor activity was declared for log cell kill < 0.7, and the treatment was declared highly active for log cell kill ≥ 2.8
- Tumor Free Survivors (TFS): correspond to complete regression below the limit of palpation (63 mg) for the entire duration of the study (>100 days post last treatment).

- Therapeutic Synergism: a combination has therapeutic synergism if it is more active than the best single agent of the study (by at least 1 log cell kill).

Toxicity for melphalan alone was observed at a dose of 16.1 mg/kg/injection, with 3 drug-related deaths out of 5 mice, i.e. above the 10 % threshold. The highest nontoxic dose (HNTD) for melphalan was 10 mg/kg/inj (total injected dose = 40 mg/kg). The 10 mg/kg/inj dose was found to be active with a log cell kill of 1.9.

Regarding hu38SB19, the product was well tolerated at a dose of 40 mg/kg/inj. No toxicity was observed, which can be explained by the lack of cross-reactivity of the antibody with murine CD38. The log cell kill was 0.5, indicating that hu38DB19 was not active under these conditions.

The combination of melphalan at 16.1 mg/kg/inj and hu38SB19 at 40 mg/kg/inj was toxic, with 5 out of 5 drug-related deaths, i.e. very similar to what was observed with melphalan alone at the same dose. The dose of 10 mg/kg/inj of melphalan with 40 mg/kg/inj of hu38SB19 was considered to be the HNTD. At this dose, the log cell kill was 2.2, indicating that the combination was as active as the best agent, i.e. melphalan.

Another experiment was performed with LP1, a human multiple myeloma model highly sensitive to melphalan in comparison to RPMI-8226. The model was implanted on SCID mice.

Hu38SB19 was formulated in glucose 5 % in water. Hu38SB19 was administered intravenously on days 12, 15, 18, 21 after tumor implantation.

Melphalan was formulated in 5 % ethanol, 5 % polysorbate 80, 90 % sodium chloride 0.9 % in water. Melphalan was administered intravenously simultaneously to hu38SB19 on days 12, 15, 18, 21 after tumor implantation.

The results of the experiment are reported in Table 2.

Tumor doubling time = 1.5 days.

The following end points have been used:

- Toxicity was declared at dosages inducing ≥ 20 % body weight loss or ≥ 10 % drug death,
- Antitumor efficacy was determined by calculation of the log10 cell kill = (T-C) / [3.32 x (tumor doubling time in days)]

(T meaning the median time of the treated mice to reach 1000 mg and C the median time (16.8 days) of the control mice to reach the same size; tumor-free survivors are excluded from these calculations and are tabulated separately). No antitumor activity was declared for log cell kill < 0.7, and the treatment was declared highly active for log cell kill ≥ 2.8

- Therapeutic Synergism: A combination has therapeutic synergism if it is more active than the best single agent of the study (by at least 1 log cell kill).

Toxicity for melphalan alone was observed at a dose of 16.1 mg/kg/injection, with 33.6 % body weight loss at nadir on day 22, i.e. above the 20 % threshold and 4/5 drug-related deaths. The HNTD for melphalan was 10 mg/kg/inj (total injected dose = 40 mg/kg). The 10 mg/kg/inj dose was found to be highly active with a 9.3 log cell kill.

Regarding hu38SB19, the product was well tolerated at a dose of 40 mg/kg/inj. No toxicity was observed, which can be explained by the lack of cross-reactivity of the antibody with murine CD38. The log cell kill was 0.2, indicating that hu38DB19 was not active under these conditions.

The combination of melphalan at 16.1 mg/kg/inj and hu38SB19 at 40 mg/kg/inj was toxic, with 34.2 % body weight loss at nadir on day 22 and 5/5 drug-related deaths, i.e. very similar to what was observed with melphalan alone at the same dose. The dose of 10 mg/kg/inj of melphalan with 40 mg/kg/inj of hu38SB19 was considered to be the highest nontoxic dose. Remarkably, this dose displayed a high antitumor efficacy of 18.9 log cell kill (and 1/5 TFS on day 148) and demonstrated therapeutic synergism in comparison to the HNTD of the melphalan alone (9.3 log cell kill). Therapeutic synergism was maintained at lower dose levels of the combination in comparison to equitoxic doses of melphalan alone.

Table I: Combination of hu38SB19 and melphalan against advanced human multiple myeloma RPMI-8226 implanted in SCID female mice.

agent, route and dose in mg/kg/inj (total dose)		Schedule in days	Drug death	% BWC at nadir (day)	T-C in days (1000 mg)	log_{10} cell kill	Comments
hu38SB19 IV	melphalan IV						
40.0 (160.0)	-	16,19,22,25	0/5	+5.3 (26)	5.2	0.5	HDT - inactive
-	16.1 (32.2)	16,19	3/5	-33.4 (26)	-	-	Toxic
-	10.0 (40.0)	16,19,22,25	0/5	-12.2 (26)	20.0	1.9	HNTD, active
-	6.2 (24.8)		0/5	-3.5 (32)	9.5	0.9	Active
-	3.8 (15.2)		0/5	-1.2 (17)	8.5	0.8	Moderately active
40.0 (80.0)	16.1 (32.2)	16,19	5/5	-30.6 (22)	-	-	Toxic
40.0 (160.0)	10.0 (40.0)	16,19,22,25	0/5	-10.0 (26)	23.6	2.2	HNTD, active
40.0 (160.0)	6.2 (24.8)		0/5	-4.0 (28)	13.6	1.3	Active
40.0 (160.0)	3.8 (15.2)		0/5	-1.9 (17)	7.5	0.7	Marginally active

Tumor doubling time = 3.2 days. Median tumor size at start of therapy = 131-148 mg. Time for median tumor to reach 1000 mg = 25.3 days. Formulation: hu38SB19 = phosphate buffer saline without Ca^{2+} and Mg^{2+}, pH 7.4; melphalan = 5 % ethanol, 5 % polysorbate 80, 90 % sodium chloride 0.9 % in water. BWC = body weight change, T-C = tumor growth delay, HNTD = highest nontoxic dose, HDT = highest dose tested, IV = intravenous.

Table II: Combination of hu38SB19 and melphalan against advanced human multiple myeloma LP1 implanted in SCID female mice.

agent, route Dose in mg/kg/inj (total dose)		Schedule in days	% BWC at nadir (day)	T-C in days (1000 mg)	log_{10} cell kill gross	Comments
hu38SB19 IV	melphalan IV					
40.0 (160.0)	-	12, 15, 18, 21	+15.9 (22)	1.1	0.2	HDT-inactive
-	16.1 (48.3)[a]	12, 15, 18, 21	-33.6 (22)	NTBA	NTBA	Toxic 4/5 deaths
-	10.0 (40.0)		-14.6 (24)	46.5	9.3	HNTD, highly active
-	6.2 (24.8)		-3.0 (24)	17.4	3.5	Highly active
-	3.8 (15.2)		+7.0 (22)	4.1	0.8	Moderately active
40.0 (120.0)[a]	16.1 (48.3)[a]	12, 15, 18, 21	-34.2 (22)	NTBA	NTBA	Toxic 5/5 deaths
40.0 (160.0)	10.0 (40.0)		-11.2 (23)	94.1	18.9	HNTD, highly active 1/5 TFS
40.0 (160.0)	6.2 (24.8)		-5.1 (25)	48.3	9.7	Highly active
40.0 (160.0)	3.8 (15.2)		-0.8 (14)	22.0	4.4	Highly active

Tumor doubling time = 1.5 days. Median tumor size at start of therapy = 111-127 mg. Time for median tumor to reach 1000 mg = 16.8 days. Formulation: hu38SB19= glucose 5 % in water, melphalan: 5 % ethanol, 5 % polysorbate 80, 90 % sodium chloride 0.9 % in water. BWC = body weight change, T-C= tumor growth delay, HNTD = highest nontoxic dose, HDT = highest dose tested, TFS = tumor free survivors, NTBA = Non tumor bearing animals, IV= intravenous.[a] treatments were stopped on day 18 when toxicity was reached.

Claims

1. A pharmaceutical combination comprising an antibody specifically recognizing CD38 and at least melphalan, wherein said antibody is capable of killing a $CD38^+$ cell by apoptosis, antibody-dependent cell-mediated cytotoxicity (ADCC), and complement-dependent cytotoxicity (CDC).

2. The combination of claim 1, wherein said antibody is a humanized antibody.

3. The combination of claim 2 wherein said antibody comprises one or more complementarity-determining region having an amino acid sequence selected from the group consisting of SEQ ID NOS: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, and 81.

4. The combination of claim 3 wherein said antibody comprises at least one heavy chain and at least one light chain, wherein said heavy chain has an amino acid sequence represented by SEQ ID NO: 66 and/or said heavy chain comprises three sequential complementarity-determining regions having amino acid sequences represented by SEQ ID NOS: 13, 81, and 15, and wherein said light chain has an amino acid sequence selected from the group of SEQ ID NOS: 62 and 64, and/or said light chain comprises three sequential complementarity-determining regions having amino acid sequences represented by SEQ ID NOS: 16, 17, and 18.

5. The combination of claim 3 wherein said antibody comprises at least one heavy chain and at least one light chain, wherein said heavy chain has an amino acid sequence represented by SEQ ID NO: 72 and said heavy chain comprises three sequential complementarity-determining regions having amino acid sequences represented by SEQ ID NOS: 25, 26, and 27, and wherein said light chain has an amino acid sequence selected from the group of SEQ ID NOS: 68 and 70, and/or said light chain comprises three sequential complementarity-determining regions having amino acid sequences represented by SEQ ID NOS: 28, 29, and 30.

6. Use of an antibody specifically recognizing CD38 and at least melphalan for the manufacture of a medicament for the treatment of cancer, wherein said antibody is capable of killing a $CD38^+$ cell by apoptosis, antibody-dependent cell-mediated cytotoxicity (ADCC), and complement-dependent cytotoxicity (CDC).

7. Use of a pharmaceutical combination according to any one or claims 1 to 5 for the manufacture of a medicament for the treatment of cancer.

8. The use of claim 6 or claim 7, wherein said antibody is a humanized antibody.

9. The use of claim 8 wherein said antibody comprises one or more complementarity-determining region having an amino acid sequence selected from the group consisting of SEQ ID NOS: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, and 81.

10. The use of claim 9 wherein said antibody comprises at least one heavy chain and at least one light chain, wherein said heavy chain has an amino acid sequence represented by SEQ ID NO: 66 and/or said heavy chain comprises three sequential complementarity-determining regions having amino acid sequences represented by SEQ ID NOS: 13, 81, and 15, and wherein said light chain has an amino acid sequence selected from the group of SEQ ID NOS: 62 and 64, and/or said light chain comprises three sequential complementarity-determining regions having amino acid sequences represented by SEQ ID NOS: 16, 17, and 18.

11. The use of claim 9 wherein said antibody comprises at least one heavy chain and at least one light chain, wherein said heavy chain has an amino acid sequence represented by SEQ ID NO: 72 and said heavy chain comprises three sequential complementarity-determining regions having amino acid sequences represented by SEQ ID NOS: 25, 26, and 27, and wherein said light chain has an amino acid sequence selected from the group of SEQ ID NOS: 68 and 70, and/or said light chain comprises three sequential complementarity-determining regions having amino acid sequences represented by SEQ ID NOS: 28, 29, and 30.

12. A combination as claimed in any one of claims 1 to 5, substantially as herein described with reference to any example thereof.

13. A use as claimed in any one of claims 6 to 11, substantially as herein described with reference to any example thereof.

SEQUENCE LISTING

<110> SANOFI-AVENTIS

<120> ANTITUMOR COMBINATIONS CONTAINING ANTIBODIES RECOGNIZING SPECIFICALLY CD38 AND MELPHALAN

<130> FR2008-111

<160> 80

<170> PatentIn version 3.3

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cag agg gcc acc ata tcc tgc aga gcc agt gaa agt gtt gag att tat       96
Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Glu Ile Tyr
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Gly Asn Gly Phe Met Asn Trp Phe Gln Gln Lys Pro Gly Gln Pro Pro
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Lys Leu Leu Ile Tyr Arg Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala
    50                  55                  60

agg ttc agt ggc agt ggg tct agg aca gag ttc acc ctc acc att gat      240
Arg Phe Ser Gly Ser Gly Ser Arg Thr Glu Phe Thr Leu Thr Ile Asp
65                  70                  75                  80

cct gtg gag gct gat gat gtt gca acc tat tac tgt caa caa att aat      288
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gag gat cca ttc acg ttc ggc tcg ggg aca aag ttg gaa ata aaa cgg      336
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Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ile Ser Val Gln Ala
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gaa gac ctg gca gtt tat tac tgt caa caa cat tat act act ccc acg      288
Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Thr
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Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Val Gln Ser
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Asp Arg Val Ser Val Thr Cys Lys Ala Ser Gln Asn Val Gly Thr Asn
            20                  25                  30

gtt gcc tgg tat caa cac aaa cca gga caa tcc cct aaa ata atg att      144
Val Ala Trp Tyr Gln His Lys Pro Gly Gln Ser Pro Lys Ile Met Ile
        35                  40                  45

tat tcg gcg tcc tcc cgg tac agt gga gtc cct gat cgc ttc aca ggc      192
Tyr Ser Ala Ser Ser Arg Tyr Ser Gly Val Pro Asp Arg Phe Thr Gly
    50                  55                  60

agt gga tct ggg aca ctt ttc act ctc acc atc aac aat gtg cag tct      240
Ser Gly Ser Gly Thr Leu Phe Thr Leu Thr Ile Asn Asn Val Gln Ser
65                  70                  75                  80

gaa gac ttg gca gag tat ttc tgt cag caa tat aac agc tat cct ctc      288
Glu Asp Leu Ala Glu Tyr Phe Cys Gln Gln Tyr Asn Ser Tyr Pro Leu
                85                  90                  95

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Tyr Ser Ala Ser Ser Arg Tyr Ser Gly Val Pro Asp Arg Phe Thr Gly
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Ser Gly Ser Gly Thr Leu Phe Thr Leu Thr Ile Asn Asn Val Gln Ser
65                  70                  75                  80

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

gga atg aac tgg gtg aag cag gct cca gga aag ggt tta aag tgg atg      144
Gly Met Asn Trp Val Lys Gln Ala Pro Gly Lys Gly Leu Lys Trp Met
        35                  40                  45

ggc tgg ata aac acc tac act gga gaa cca aca tat gct gat gac ttt      192
Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe
    50                  55                  60

aag gga cgt ttt gcc ttc tct ttg gaa acc tct gcc agc act gcc ttt      240
Lys Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Phe
65                  70                  75                  80

ttg cag atc aac aac ctc aaa aat gag gac acg gct aca tat ttc tgt      288
Leu Gln Ile Asn Asn Leu Lys Asn Glu Asp Thr Ala Thr Tyr Phe Cys
                85                  90                  95

gta aga cgc ggg ttt gct tac tgg ggc caa ggg act ctg gtc act gtc      336
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Gly Met Asn Trp Val Lys Gln Ala Pro Gly Lys Gly Leu Lys Trp Met
        35                  40                  45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe
    50                  55                  60

Lys Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Phe
65                  70                  75                  80
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Leu Gln Ile Asn Asn Leu Lys Asn Glu Asp Thr Ala Thr Tyr Phe Cys
                85                  90                  95

Val Arg Arg Gly Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
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aca gtc aag atc tcc tgc aag gct tct ggg tat acc ttc aca aac tct       96
Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Ser
            20                  25                  30

gga atg aac tgg gtg aag cag gct cca gga aag ggt tta aag tgg atg      144
Gly Met Asn Trp Val Lys Gln Ala Pro Gly Lys Gly Leu Lys Trp Met
        35                  40                  45

ggc tgg ata aac acc tac act gga gag ccg aca tat gct gat gac ttc      192
Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe
    50                  55                  60

aag gga cgg ttt gcc ttc tct ttg gaa acc tct gcc agc tct gcc tat      240
Lys Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Ser Ala Tyr
65                  70                  75                  80

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                85                  90                  95

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

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

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe
    50                  55                  60

Lys Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Ser Ala Tyr
65                  70                  75                  80

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

Ala Arg Arg Gly Phe Val Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
            100                 105                 110

Ser Ala
```

<210> 53
<211> 360
<212> DNA
<213> Mus sp.

<220>
<221> CDS
<222> (1)..(360)

<400> 53

```
cag gtt cag ctc cag cag tct ggg gct gag ctg gca aga cct ggg act       48
Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Arg Pro Gly Thr
1               5                   10                  15

tca gtg aag ttg tcc tgt aag gct tct ggc tac acc ttt act gac tac       96
Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
            20                  25                  30

tgg atg cag tgg gta aaa cag agg cct gga cag ggt ctg gag tgg att      144
Trp Met Gln Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

ggg act att tat cct gga gat ggt gat act ggg tac gct cag aag ttc      192
Gly Thr Ile Tyr Pro Gly Asp Gly Asp Thr Gly Tyr Ala Gln Lys Phe
    50                  55                  60

aag ggc aag gcc aca ttg act gcg gat aaa tcc tcc aaa aca gtc tac      240
Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Lys Thr Val Tyr
65                  70                  75                  80

atg cac ctc agc agt ttg gct tct gag gac tct gcg gtc tat tac tgt      288
Met His Leu Ser Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95

gca aga ggg gat tac tac ggt agt aat tct ttg gac tat tgg ggt caa      336
Ala Arg Gly Asp Tyr Tyr Gly Ser Asn Ser Leu Asp Tyr Trp Gly Gln
            100                 105                 110
```

gga acc tca gtc acc gtc tcc tca 360
Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 54
<211> 120
<212> PRT
<213> Mus sp.

<400> 54

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

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

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

Gly Thr Ile Tyr Pro Gly Asp Gly Asp Thr Gly Tyr Ala Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Lys Thr Val Tyr
65 70 75 80

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

Ala Arg Gly Asp Tyr Tyr Gly Ser Asn Ser Leu Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 55
<211> 357
<212> DNA
<213> Mus sp.

<220>
<221> CDS
<222> (1)..(357)

<400> 55
cag gtc cag tta cag caa tct gga cct gaa ctg gtg agg cct ggg gcc 48
Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Arg Pro Gly Ala
1 5 10 15

tca gtg aag att tcc tgc aaa act tct ggc tac gca ttc agt ggc tcc 96
Ser Val Lys Ile Ser Cys Lys Thr Ser Gly Tyr Ala Phe Ser Gly Ser
20 25 30

tgg atg aac tgg gtg aag cag agg cct gga cag ggt cta gag tgg att 144
Trp Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

gga cgg att tat ccg gga gat gga gat atc att tac aat ggg aat ttc 192

```
Gly Arg Ile Tyr Pro Gly Asp Gly Asp Ile Ile Tyr Asn Gly Asn Phe
    50                  55                  60

agg gac aag gtc aca ctg tct gca gac aaa tcc tcc aac aca gcc tac      240
Arg Asp Lys Val Thr Leu Ser Ala Asp Lys Ser Ser Asn Thr Ala Tyr
65                  70                  75                  80

atg cag ctc agc agc ctg acc tct gtg gac tct gcg gtc tat ttt tgt      288
Met Gln Leu Ser Ser Leu Thr Ser Val Asp Ser Ala Val Tyr Phe Cys
                85                  90                  95

tcg aga tgg ggg aca ttt acg ccg agt ttt gac tat tgg ggc caa ggc      336
Ser Arg Trp Gly Thr Phe Thr Pro Ser Phe Asp Tyr Trp Gly Gln Gly
            100                 105                 110

acc act ctc aca gtc tcc tca                                         357
Thr Thr Leu Thr Val Ser Ser
        115


<210>  56
<211>  119
<212>  PRT
<213>  Mus sp.

<400>  56

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

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

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

Gly Arg Ile Tyr Pro Gly Asp Gly Asp Ile Ile Tyr Asn Gly Asn Phe
    50                  55                  60

Arg Asp Lys Val Thr Leu Ser Ala Asp Lys Ser Ser Asn Thr Ala Tyr
65                  70                  75                  80

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

Ser Arg Trp Gly Thr Phe Thr Pro Ser Phe Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Thr Leu Thr Val Ser Ser
        115


<210>  57
<211>  351
<212>  DNA
<213>  Mus sp.


<220>
<221>  CDS
<222>  (1)..(351)
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<400> 57
gac gtg aag ctg gtg gag tct ggg gga ggc tta gtg aag cct gga ggg 48
Asp Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

tcc ctg aaa ctc tcc tgt gaa gcc tct gga ttc act ttc agt agc tat 96
Ser Leu Lys Leu Ser Cys Glu Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

acc ctg tct tgg gtt cgc cag act ccg gag acg agg ctg gag tgg gtc 144
Thr Leu Ser Trp Val Arg Gln Thr Pro Glu Thr Arg Leu Glu Trp Val
35 40 45

gca acc att agt att ggt ggt cgc tac acc tat tat cca gac agt gtg 192
Ala Thr Ile Ser Ile Gly Gly Arg Tyr Thr Tyr Tyr Pro Asp Ser Val
50 55 60

gag ggc cga ttc acc atc tcc aga gac aat gcc aag aac acc ctg tac 240
Glu Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65 70 75 80

ctg caa atg aac agt ctg aag tct gag gac aca gcc atg tat tac tgt 288
Leu Gln Met Asn Ser Leu Lys Ser Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95

aca aga gat ttt aat ggt tac tct gac ttc tgg ggc caa ggc acc act 336
Thr Arg Asp Phe Asn Gly Tyr Ser Asp Phe Trp Gly Gln Gly Thr Thr
100 105 110

ctc aca gtc tcc tca 351
Leu Thr Val Ser Ser
115

<210> 58
<211> 117
<212> PRT
<213> Mus sp.

<400> 58

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

Ser Leu Lys Leu Ser Cys Glu Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Thr Leu Ser Trp Val Arg Gln Thr Pro Glu Thr Arg Leu Glu Trp Val
35 40 45

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

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

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

Thr Arg Asp Phe Asn Gly Tyr Ser Asp Phe Trp Gly Gln Gly Thr Thr
100 105 110

Leu Thr Val Ser Ser
115

<210> 59
<211> 360
<212> DNA
<213> Mus sp.

<220>
<221> CDS
<222> (1)..(360)

<400> 59
aat gta cag ctg gta gag tct ggg gga ggc tta gtg cag cct gga ggg 48
Asn Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

tcc cgg aaa ctc tcc tgt gca gcc tct gga ttc act ttc agt aac ttt 96
Ser Arg Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Phe
20 25 30

gga atg cac tgg gtt cgt cag gct cca gag aag ggt ctg gag tgg gtc 144
Gly Met His Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
35 40 45

gca tac att cgt agt ggc agt ggt acc atc tac tat tca gac aca gtg 192
Ala Tyr Ile Arg Ser Gly Ser Gly Thr Ile Tyr Tyr Ser Asp Thr Val
50 55 60

aag ggc cga ttc acc atc tcc aga gac aat ccc aag aac acc ctg ttc 240
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Pro Lys Asn Thr Leu Phe
65 70 75 80

ctg caa atg acc agt cta agg tct gag gac acg gcc atg tat tac tgt 288
Leu Gln Met Thr Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95

gca aga tcc tac tat gat ttc ggg gcc tgg ttt gct tac tgg ggc caa 336
Ala Arg Ser Tyr Tyr Asp Phe Gly Ala Trp Phe Ala Tyr Trp Gly Gln
100 105 110

ggg act ctg gtc act gtc tct gca 360
Gly Thr Leu Val Thr Val Ser Ala
115 120

<210> 60
<211> 120
<212> PRT
<213> Mus sp.

<400> 60

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

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

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

```
Ala Tyr Ile Arg Ser Gly Ser Gly Thr Ile Tyr Tyr Ser Asp Thr Val
    50                  55                  60

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

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

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

Gly Thr Leu Val Thr Val Ser Ala
        115                 120
```

<210> 61
<211> 324
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(324)

<400> 61

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gat atc gta atg acc cag tcc cac ctg agt atg agt acc tcc ctg gga       48
Asp Ile Val Met Thr Gln Ser His Leu Ser Met Ser Thr Ser Leu Gly
1               5                   10                  15

gat cct gtg tca atc act tgc aag gcc tca cag gat gtg agc acc gtc       96
Asp Pro Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Thr Val
            20                  25                  30

gtt gct tgg tat cag cag aag ccc ggg caa tca ccc aga cgt ctc atc      144
Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Arg Arg Leu Ile
        35                  40                  45

tac tca gca tca tac cgt tac atc ggg gtg cct gac cga ttt act ggc      192
Tyr Ser Ala Ser Tyr Arg Tyr Ile Gly Val Pro Asp Arg Phe Thr Gly
    50                  55                  60

tct ggc gct ggc aca gat ttc acc ttt aca att agt tcc gtc cag gcc      240
Ser Gly Ala Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Val Gln Ala
65                  70                  75                  80

gaa gac ctg gcc gtg tac tac tgc cag cag cac tac agt ccc cca tac      288
Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln His Tyr Ser Pro Pro Tyr
                85                  90                  95

act ttc ggg gga ggg act aag ctc gaa atc aaa cgt                     324
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
            100                 105
```

<210> 62
<211> 108
<212> PRT
<213> Homo sapiens

<400> 62

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

Asp Pro Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Thr Val
            20                  25                  30

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

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

Ser Gly Ala Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Val Gln Ala
65                  70                  75                  80

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

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

<210> 63
<211> 324
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(324)

<400> 63

```
gac att gtt atg gct caa agc cat ctg tct atg agc aca tct ctg gga       48
Asp Ile Val Met Ala Gln Ser His Leu Ser Met Ser Thr Ser Leu Gly
1               5                   10                  15

gat cct gtg tcc atc act tgc aaa gcc agt caa gac gtg tct aca gtt       96
Asp Pro Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Thr Val
            20                  25                  30

gtt gca tgg tat caa cag aag cca ggc cag tca ccc aga cgg ctc att      144
Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Arg Arg Leu Ile
        35                  40                  45

tac tca gct tct tac cga tac atc ggg gtc cct gac aga ttt aca ggt      192
Tyr Ser Ala Ser Tyr Arg Tyr Ile Gly Val Pro Asp Arg Phe Thr Gly
    50                  55                  60

agt ggg gcc ggt act gac ttc act ttt act atc tca tcc gta caa gcc      240
Ser Gly Ala Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Val Gln Ala
65                  70                  75                  80

gaa gac ctg gca gta tat tac tgc cag caa cat tat tcc cca ccc tac      288
Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln His Tyr Ser Pro Pro Tyr
                85                  90                  95

aca ttc ggc ggg ggt act aag ctg gaa att aaa cgt                      324
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
            100                 105
```

<210> 64
<211> 108
<212> PRT
<213> Homo sapiens

<400> 64

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

Asp Pro Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Thr Val
20 25 30

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

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

Ser Gly Ala Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Val Gln Ala
65 70 75 80

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

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

<210> 65
<211> 360
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(360)

<400> 65

cag gta cag ctc gtt cag tcc ggc gcc gag gta gct aag cct ggt act 48
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Ala Lys Pro Gly Thr
1 5 10 15

tcc gta aaa ttg tcc tgt aag gct tcc ggg tac aca ttt aca gac tac 96
Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

tgg atg cag tgg gta aaa cag cgg cca ggt cag ggc ctg gag tgg att 144
Trp Met Gln Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

gga aca ata tat ccc ggc gac ggc gac aca ggc tat gcc cag aag ttt 192
Gly Thr Ile Tyr Pro Gly Asp Gly Asp Thr Gly Tyr Ala Gln Lys Phe
50 55 60

caa ggc aag gca acc ctt act gct gat aaa tct tcc aag act gtc tac 240
Gln Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Lys Thr Val Tyr
65 70 75 80

atg cat ctg tct tcc ttg gca tct gag gat agc gct gtc tat tac tgt 288
Met His Leu Ser Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Tyr Cys

85 90 95

gct agg ggg gac tac tat ggg tca aat tcc ctg gat tac tgg ggc cag 336
Ala Arg Gly Asp Tyr Tyr Gly Ser Asn Ser Leu Asp Tyr Trp Gly Gln
100 105 110

ggc acc agt gtc acc gtg agc agc 360
Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 66
<211> 120
<212> PRT
<213> Homo sapiens

<400> 66

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

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

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

Gly Thr Ile Tyr Pro Gly Asp Gly Asp Thr Gly Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Lys Thr Val Tyr
65 70 75 80

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

Ala Arg Gly Asp Tyr Tyr Gly Ser Asn Ser Leu Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 67
<211> 324
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(324)

<400> 67
gac acc gtg atg acc cag tcc ccc tcc acc atc tcc acc tct gtg ggc 48
Asp Thr Val Met Thr Gln Ser Pro Ser Thr Ile Ser Thr Ser Val Gly
1 5 10 15

gac cgg gtg tcc atc acc tgt aag gcc tcc cag gtg gtg ggc tcc gcc 96
Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Val Val Gly Ser Ala
20 25 30

```
gtg gcc tgg tat cag cag aag cct ggc cag tcc cct aag ctg ctg atc      144
Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
        35                  40                  45

tac tgg gcc tcc acc cgg cat acc ggc gtg cct gac cgg ttc acc ggc      192
Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Asp Arg Phe Thr Gly
    50                  55                  60

tcc ggc agc ggc acc gac ttc acc ctg acc atc tcc aac gtg cag tcc      240
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Val Gln Ser
65                  70                  75                  80

gac gac ctg gcc gac tac ttc tgc cag cag tac aac tcc tac cct tac      288
Asp Asp Leu Ala Asp Tyr Phe Cys Gln Gln Tyr Asn Ser Tyr Pro Tyr
                85                  90                  95

acc ttt ggc ggc gga aca aag ctg gag atc aag cgt                      324
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
            100                 105
```

<210> 68
<211> 108
<212> PRT
<213> Homo sapiens

<400> 68

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

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

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

Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Asp Arg Phe Thr Gly
    50                  55                  60

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

Asp Asp Leu Ala Asp Tyr Phe Cys Gln Gln Tyr Asn Ser Tyr Pro Tyr
                85                  90                  95

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

<210> 69
<211> 324
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(324)

<400> 69

```
gac acc gtg atg acc cag tcc ccc tcc tcc atc tcc acc tcc atc ggc       48
Asp Thr Val Met Thr Gln Ser Pro Ser Ser Ile Ser Thr Ser Ile Gly
1               5                   10                  15

gac cgg gtg tcc atc acc tgt aag gcc tcc cag gtg gtg ggc tcc gcc       96
Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Val Val Gly Ser Ala
            20                  25                  30

gtg gcc tgg tat cag cag aag cct ggc cag tcc cct aag ctg ctg atc      144
Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
        35                  40                  45

tac tgg gcc tcc acc cgg cat acc ggc gtg cct gcc cgg ttc acc ggc      192
Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Ala Arg Phe Thr Gly
    50                  55                  60

tcc ggc agc ggc acc gac ttc acc ctg acc atc tcc aac gtg cag tcc      240
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Val Gln Ser
65                  70                  75                  80

gag gac ctg gcc gac tac ttc tgc cag cag tac aac tcc tac cct tac      288
Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln Tyr Asn Ser Tyr Pro Tyr
                85                  90                  95

acc ttt ggc ggc gga aca aag ctg gag atc aag cgt                      324
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
            100                 105
```

<210> 70
<211> 108
<212> PRT
<213> Homo sapiens

<400> 70

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

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

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

Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Ala Arg Phe Thr Gly
    50                  55                  60

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

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

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

<210> 71
<211> 351
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(351)

<400> 71
gag gtg cag ctg gtg gag tct ggc ggc gga ctg gtg aag cct ggc ggc 48
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

tcc ctg agg ctg tcc tgt gag gcc tcc ggc ttc acc ttc tcc tcc tac 96
Ser Leu Arg Leu Ser Cys Glu Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

acc ctg tcc tgg gtg agg cag acc cct ggc aag ggc ctg gag tgg gtg 144
Thr Leu Ser Trp Val Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

gcc acc atc tcc atc ggc ggc agg tac acc tac tac cct gac tcc gtg 192
Ala Thr Ile Ser Ile Gly Gly Arg Tyr Thr Tyr Tyr Pro Asp Ser Val
50 55 60

aag ggc cgg ttc acc atc tcc cgg gac aac gcc aag aac acc ctg tac 240
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65 70 75 80

ctg cag atg aac tcc ctg aag tcc gag gac acc gcc atg tac tac tgt 288
Leu Gln Met Asn Ser Leu Lys Ser Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95

acc cgg gac ttc aac ggc tac tcc gac ttc tgg ggc cag ggc acc aca 336
Thr Arg Asp Phe Asn Gly Tyr Ser Asp Phe Trp Gly Gln Gly Thr Thr
100 105 110

ctg acc gtg tcc tcc 351
Leu Thr Val Ser Ser
115

<210> 72
<211> 117
<212> PRT
<213> Homo sapiens

<400> 72

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

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

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

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

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

Leu Gln Met Asn Ser Leu Lys Ser Glu Asp Thr Ala Met Tyr Tyr Cys

85 90 95

Thr Arg Asp Phe Asn Gly Tyr Ser Asp Phe Trp Gly Gln Gly Thr Thr
100 105 110

Leu Thr Val Ser Ser
115

<210> 73
<211> 36
<212> DNA
<213> Mus sp.

<400> 73
ggaggatcca tagacagatg ggggtgtcgt tttggc 36

<210> 74
<211> 32
<212> DNA
<213> Mus sp.

<400> 74
ggaggatccc ttgaccaggc atcctagagt ca 32

<210> 75
<211> 32
<212> DNA
<213> Mus sp.

<220>
<221> misc_feature
<222> (1)..(32)
<223> mixed bases are defined as follows: H=A+T+C, S=G+C, Y=C+T, K=
G+T, M=A+C, R=A+G, W=A+T, V = A+C+G, N = A+C+G+T

<400> 75
cttccggaat tcsargtnma gctgsagsag tc 32

<210> 76
<211> 35
<212> DNA
<213> Mus sp.

<220>
<221> misc_feature
<222> (1)..(35)
<223> mixed bases are defined as follows: H=A+T+C, S=G+C, Y=C+T, K=
G+T, M=A+C, R=A+G, W=A+T, V = A+C+G, N = A+C+G+T

<400> 76
cttccggaat tcsargtnma gctgsagsag tcwgg 35

<210> 77
<211> 31
<212> DNA
<213> Mus sp.

<220>

<221> misc_feature
<222> (1)..(31)
<223> mixed bases are defined as follows: H=A+T+C, S=G+C, Y=C+T, K= G+T, M=A+C, R=A+G, W=A+T, V = A+C+G, N = A+C+G+T

<400> 77
ggagctcgay attgtgmtsa cmcarwctmc a 31

<210> 78
<211> 46
<212> DNA
<213> Mus sp.

<400> 78
tatagagctc aagcttggat ggtgggaaga tggatacagt tggtgc 46

<210> 79
<211> 21
<212> DNA
<213> Mus sp.

<400> 79
atggagtcac agattcaggt c 21

<210> 80
<211> 32
<212> DNA
<213> Mus sp.

<400> 80
ttttgaattc cagtaacttc aggtgtccac tc 32